“STUDY OF PULMONARY MANIFESTATIONS IN ANKYLOSING SPONDYLITIS ”

Dissertation submitted in

Partial fulfillment of the regulations required for the award of

M.D. DEGREE

In

MEDICINE – BRANCH I

THE TAMILNADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

This is to certify that the dissertation entitle **"STUDY ON PULMONARY MANIFESTATIONS IN ANKYLOSING SPONDYLITIS"** is a record of bonafide work done by **Dr.R.NITHYA KALYANI** in the Department of Medicine, Coimbatore Medical College, Coimbatore under the guidance and supervision of **Dr.S.USHA, M.D**., Professor, Department of Medicine, Coimbatore Medical College and submitted in partial fulfilment of the requirements for the award of M.D. Degree (Branch III) in Medicine by The TamilnaduDr. MGR Medical University, Chennai.

Guide
Dr.S.USHA. M.D
Professor,
Department of Medicine,
Coimbatore medical college & Hospital,
Coimbatore.

Head of the Department
Dr.KUMAR NATARAJAN
Professor,
Department of Medicine,
Coimbatore medical college & Hospital,
Coimbatore.

Dr. S. EDWIN JOE, M.D., B.L.,
The Dean,
Coimbatore medical college,
Coimbatore.

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : DR. R. NITHYAKALYANI

Course : MD - GENERAL MEDICINE

Period of Study : 2013 - 2016

College : COIMBATORE MEDICAL COLLEGE

Dissertation Topic : STUDY ON PULMONARY MANIFESTATION IN ANKYLOSING SPONDYLITIS.

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted / ~~Not accepted~~ and you are permitted / ~~Not permitted~~ to proceed with the above Study.

DEAN

Coimbatore Medical College & Hospital, Coimbatore

9.7.2014

turnitin

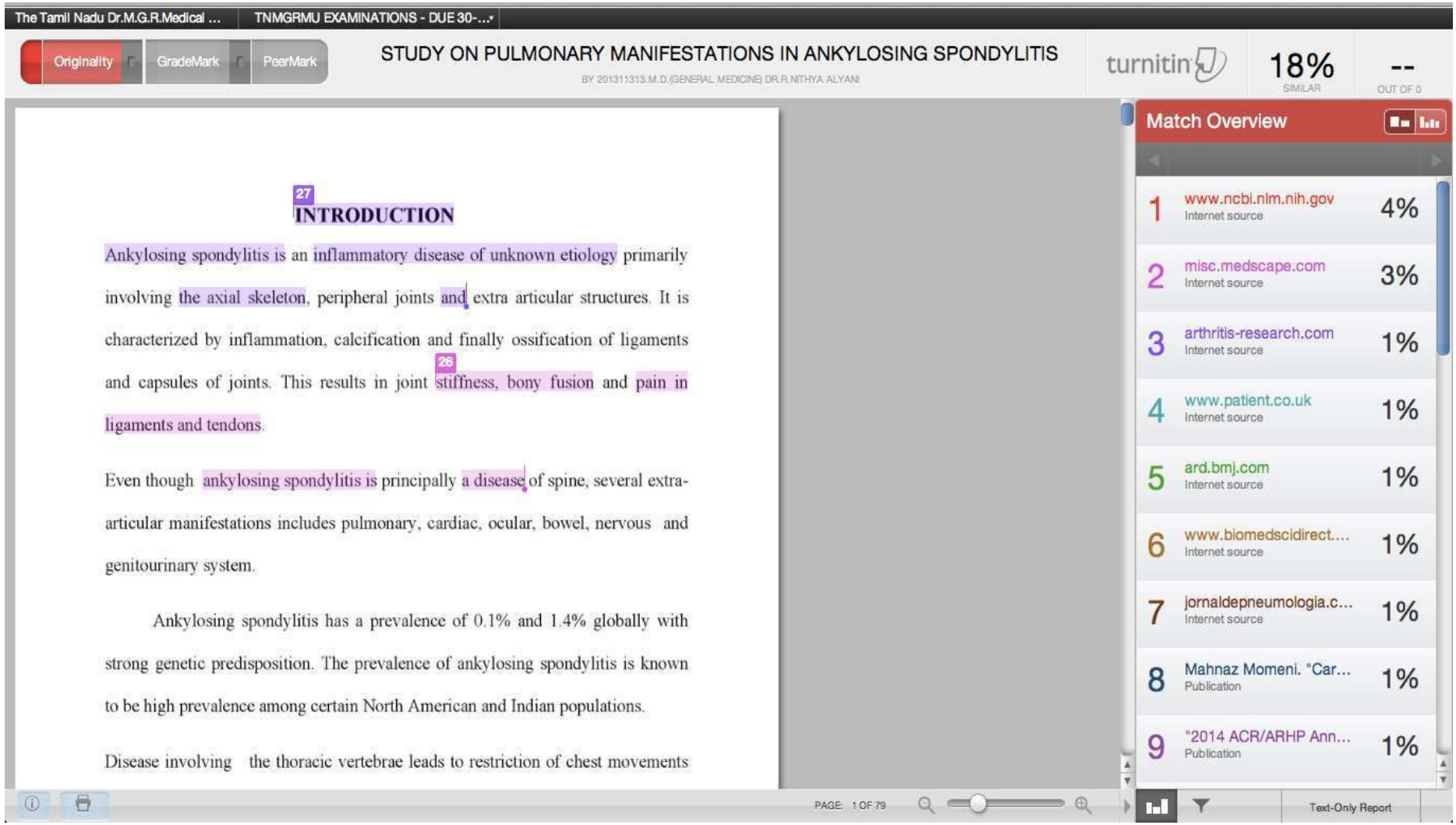
Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201311313.m.d.(general Medicine) D.
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	STUDY ON PULMONARY MANIFES...
File name:	Thesis_Copy_2.docx
File size:	2.68M
Page count:	79
Word count:	8,478
Character count:	48,434
Submission date:	23-Sep-2015 08:13AM
Submission ID:	573484350

INTRODUCTION


The Tamil Nadu Dr.M.G.R.Medical ...
TNMGRMU EXAMINATIONS - DUE 30-...
Originality
GradeMark
PeerMark
STUDY ON PULMONARY MANIFESTATIONS IN ANKYLOSING SPONDYLITIS
BY 201311313.M.D.(GENERAL MEDICINE) DR.R.NITHYA ALYANI
turnitin
18%
SIMILAR
--
OUT OF 0
27
INTRODUCTION
Ankylosing spondylitis is an inflammatory disease of unknown etiology primarily involving the axial skeleton, peripheral joints and extra articular structures. It is characterized by inflammation, calcification and finally ossification of ligaments and capsules of joints. This results in joint 26 stiffness, bony fusion and pain in ligaments and tendons.
Even though ankylosing spondylitis is principally a disease of spine, several extra-articular manifestations includes pulmonary, cardiac, ocular, bowel, nervous and genitourinary system.
Ankylosing spondylitis has a prevalence of 0.1% and 1.4% globally with strong genetic predisposition. The prevalence of ankylosing spondylitis is known to be high prevalence among certain North American and Indian populations.
Disease involving the thoracic vertebrae leads to restriction of chest movements
PAGE: 1 OF 79
Match Overview
1 www.ncbi.nlm.nih.gov Internet source 4%
2 misc.medscape.com Internet source 3%
3 arthritis-research.com Internet source 1%
4 www.patient.co.uk Internet source 1%
5 ard.bmj.com Internet source 1%
6 www.biomedscidirect.... Internet source 1%
7 jornaldepneumologia.c... Internet source 1%
8 Mahnaz Momeni. "Car... Publication 1%
9 "2014 ACR/ARHP Ann... Publication 1%
Text-Only Report

DECLARATION

I hereby declare that the dissertation entitled **"STUDY ON PULMONARY MANIFESTATIONS IN ANKYLOSING SPONDYLITIS"** is a bonafide research work done by me in the Department of Medicine, Coimbatore Medical College, during the period from July 2014 to July 2015 under the guidance and supervision of **Dr. S. USHA, M.D**., Professor , Department of Medicine, Coimbatore Medical College.

This dissertation is submitted to The TamilnaduDr. MGR Medical University, Chennai towards the partial fulfilment of the requirement for the award of M.D., Degree (Branch I) in Medicine. I have not submitted this dissertation on any previous occasion to any University for the award of any Degree.

Place: Coimbatore

Date: **Dr.R.NITHYA KALYANI**

ACKNOWLEDGEMENT

To begin with, I thank the Almighty in making this project a successful one.

I express my deep gratitude to **Dr. S.EDWIN JOE M.D.,** Dean, Coimbatore Medical College, for permitting me to undertake this study.

I am extremely grateful to **Dr.KUMARNATARAJAN ,M.D.**, for his invaluable suggestions, constant encouragement and support during this endurable work.

I express my sincere gratitude to **Dr.S.USHA, M.D.,** Professor, Department of Medicine, Coimbatore Medical College, for having suggested this topic for dissertation and for having rendered his valuable support and encouragement without which this project work would not have been feasible.

I sincerely thank **Dr.S.KEERTHIVASAN, MD., Dr.A.MAHESHDM., Dr. P.BALAMURUGAN, MD., Dr.V.USHA PADMINI MD.,** for their guidance and kind help. I sincerely thank all the patients who have submitted themselves for this study and made it possible.

I also wish to record my sincere thanks to all Associate and Assistant Professors of Department of Medicine, Coimbatore Medical College, for their constant support and encouragement throughout the work.

I thank all the technical staffs in the Department of Medicine, Coimbatore Medical College, for their sincere and timely technical assistance.

I express my heartfelt thanks to Department of Rheumatology, and Department of thoracic medicine, Coimbatore Medical College, for their constant support throughout the course of this study.

I express my heartfelt thanks and gratitude to my parents, my husband, my in laws and my lovable sister for their extreme patience, constant support, encouraging words and source of strength all the way through this endeavour.

TABLE OF CONTENTS

LIST OF ABBREVATIONS USED

AS	:	Ankylosing spondylitis
ASAS	:	Assessment of
SpA	:	Spondyloarthropathy
ILD	:	Interstitial lung disease
UIP	:	Usual Interstitial Pneumonia
PFT	:	Pulmonary function test
ESR	:	Erythrocyte Sedimentation Rate
CRP	:	C-Reactive Protein
HRCT	:	High Resolution Computed Tomography
NK cells	:	Natural Killer cells
CT	:	Computed Tomography
HLA	:	Humanleucocyteantigen
MRI	:	Magnetic Resonance Imaging
TNF - alpha	:	Tumor Necrosis Factor– alpha
TGF- beta	:	Transforming Growth Factor–beta
MHC	:	Major Histocompability complex
IL-6	:	Interleukin – 6
AV Node	:	Atrioventricular Node
TLC	:	Total Lung Capacity
RV	:	Residual Volume
VC	:	Vital Capacity
FVC	:	Forced Vital Capacity
FEV1	:	Forced Expiratory Volume 1
NSAIDS	:	Nonsteriodal anti-inflammatory drugs
PEF	:	Peak Expiratory Flow
TB	:	Tuberculosis
U/L	:	Unilateral
B/L	:	Bilateral

INTRODUCTION

Ankylosing spondylitis is an inflammatory disease of unknown etiology primarily involving the axial skeleton, peripheral joints and extra articular structures. It is characterized by inflammation, calcification and finally ossification of ligaments and capsules of joints. This results in joint stiffness, bony fusion and pain in ligaments and tendons.

Even though ankylosing spondylitis is principally a disease of spine, several extra- articular manifestations includes pulmonary, cardiac, ocular, bowel, nervous and genitourinary system.

Ankylosing spondylitis has a prevalence of 0.1% and 1.4% globally with strong genetic predisposition. The prevalence of ankylosing spondylitis is known to be high prevalence among certain North American and Indian populations.

Disease involving the thoracic vertebrae leads to restriction of chest movements due to fibrosis of spinal joints .The restriction of the chest movements leads to reduction of the lung compliance .Many studies have been done in the articular manifestation of the disease over the past decades, but very few studies have been done in the extra articular manifestation like pulmonary .

Pulmonary manifestation occurs in the late course of the disease and not in the early stage .Studies done in the pulmonary involvement of the disease showed it either involved pulmonary parenchyma manifesting as interstitial lung disease or it can involve the thoracic spine leading to deformity causing restrictive lung disease.Newer techniques like HRCT lung reveals subclinical lung disease like upper lobe fibrosis ,interstitial lung diseaseand other bullous disease and pulmonary function test which is a very simpler method, that reveals even milder restrictive impairment of the lung. Therefore pulmonary function test and HRCT lung if done in ankylosing spondylitis patients, reveals early involvement and this will improve the well - being of these patients.

AIMS AND OBJECTIVES

AIM:

- To analyse the prevalence of pulmonary manifestations in patients with ankylosing spondylitis.

OBJECTIVES:

- To observe the pulmonary manifestations in patients with ankylosing spondylitis by pulmonary function test and high resolution computerized tomography, collect data and to analyses the same.
- To investigate the correlation between ankylosing spondylitis and pulmonary disease.
- To find out the relation, if any, between pulmonary lesions with the degree, severity and the duration of ankylosing spondylitis.

REVIEW OF LITERATURE

HISTORICAL ASPECTS

RealdoColombo, provided an anatomical description of typical skeletal abnormalities of ankylosing spondylitis in his book De Re Anatomica. VonBechterew's classic description of the disease gave rise the term Bechterew'sdisease, used most commonly in Germany.

In 1930,roentgenographic manifestations including sacrolitisin early disease andsyndesmophytes in advanced disease were described by Krebs, Scott,ForestierandRobert, which helped in the diagnosis and staging of the disease still today.

MOLL et al introduced the concept of spondyloarthropathies(Spas), as a family of interrelated disorders which shares clinical and genetic characteristics distinct from rheumatoid arthritis.

In 1940-50, medical historians consider the discovery of the human leucocyte antigens (HLA) and the contribution to the understanding of the spondyloarthropathies.

Ankylosing spondylitis came as a distinct arthritic entity on the basis of 2 cases repported at London hospital with spinal immobility and back and joint pain in 1824 and 1832.

Pierre Marie (1853-1940) has given the detailed clinical description of ankylosing spondylitis and coined the word “spondyloserhizomelique”, gave detailed description of six male patients. It was fraenkel who coined the term “ankylosing spondylitis” in 1904.

Initially, it was in 1930 six cases of aortic incompetence found in a group of patient with ankylosing spondylitis. Bechterew observation of a mother and daughter favored him for genetic predisposition and neurological involvement of the disease.

Pulmonary involvement in ankylosing spondylitis was first described in1941 in an article reviewing 20 cases of ankylosing spondylitis, where 2 cases noted to have healed apical fibrosis.

High resolution computerized tomography was first utilized by casserly et al. in 1997 to evaluate lung involvement in ankylosing spondylitis patients meeting the New york criteria for ankylosing spondylitis.

EPIDEMIOLOGY

The prevalence of ankylosing spondylitis varies from country to country and is based on HLA-B27 prevalence[1]. The prevalence of the disease varies 0.1 to 1.4% globally. In population surveys 10-30% in B 27 adult first degree relatives of ASprobands and 1-6% in B27 inheritance. Its prevalence is increased in Pima and haida Indians.

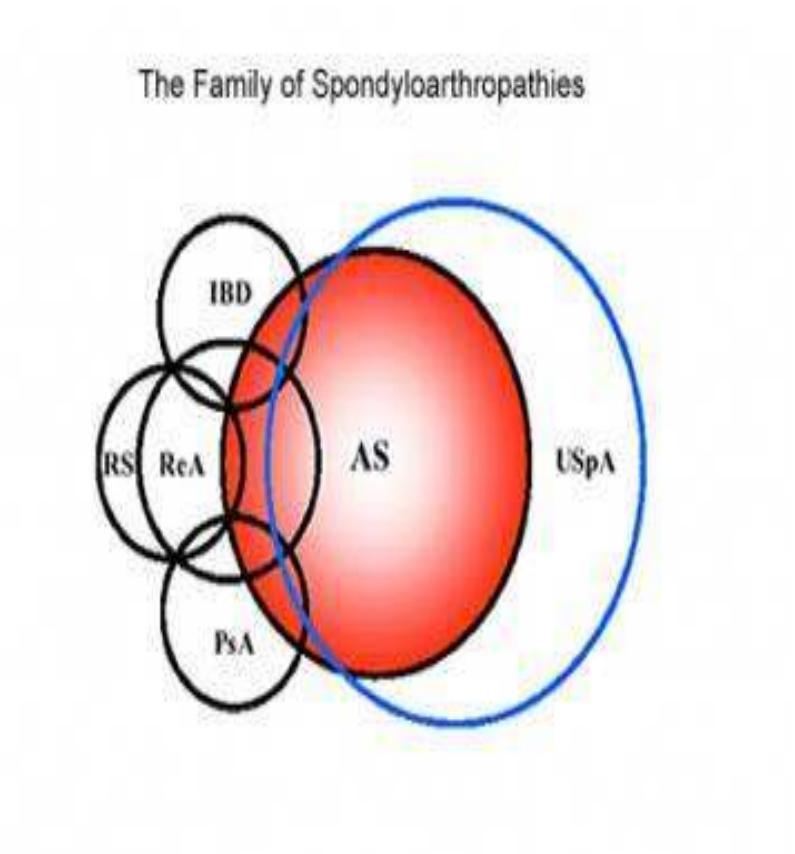
Diseases most commonly occur in late adolescence or early adulthood[1]. It also occur in children but very uncommon after 45 years of age. It commonly affects both male and female in the second or third decade[1]. The prevalence of the disease in the male: female ratio as 2:1and 3:1[4]. Over all disease manifestation tends to be more severe in men compared to that of women.

The occurrence of the disease is mainly based on genetic factors (HLA-B27) and other HLA- linked genes susceptible to AS are identified by genome-wide single-nucleotide polymorphism analysis. The genes coding for the disease are TNFSF15, TNFSF1A, STAT3, ANTXR2 and IL1R2.[1]

Ankylosing spondylitis belongs to a group of disease referred to as spondylarthropathies (SpA)[9]. SpA includes rheumatoid factor negative patients with inflammatory back and asymmetric synovitis like psoriatic

arthritis, inflammatory bowel disease and reactive arthritis.SpA is diagnosed by fulfilling the European spondylarthopathy study group, which includes positive family history, inflammatory spinal pain or synovitis.

Figure :1 Family of Spondyloarthropathies.



ETIOLOGY

The cause of AS is multifactorial and the exact etiology of ankylosing spondylitis is not known, mainly it is genetically inherited.Endogenous factor such as HLA-B27 and exogenous factor such as bacterial infections[5].

ENDOGENOUS FACTORS

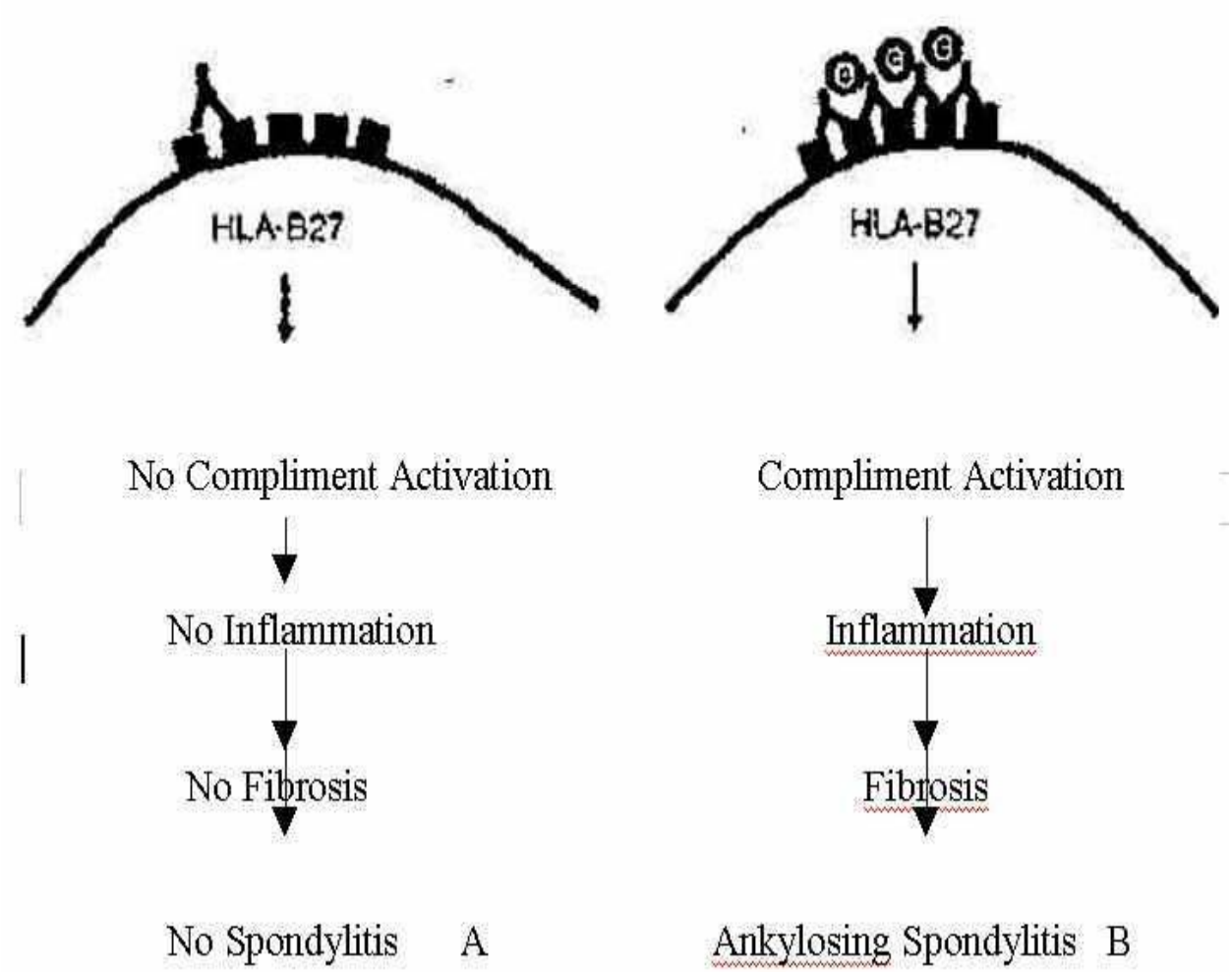
Hereditary inheritance plays a major role and familial recurrence of the disease is very high.HLA-B27 is closely related and its inheritance is about 90% in monozygous twins, 63% of them are first degree relatives and 82%are second degree. 10% of other genes involved in this disease are IL-23R andARTS1. Another gene, CARD 15 and human transforming growth factor B1(TGFB1)

EXOGENOUS FACTORS

Environmental factors also play a major role in the causes of AS.Biomedical stress plays very important role in this disease. Even though the primary pathology is inflammatory and the infective microbes play an important role in the triggering factor for the disease[6]. The innate immunity is disturbed and makes abnormal reactions following bacterial infections.

The main microorganism involved in this disease isChlamydia, enterobacter and cytokeratin[7]. Once the immune system is activated it cannot be stopped the disease process continues even though the infection is subsided.

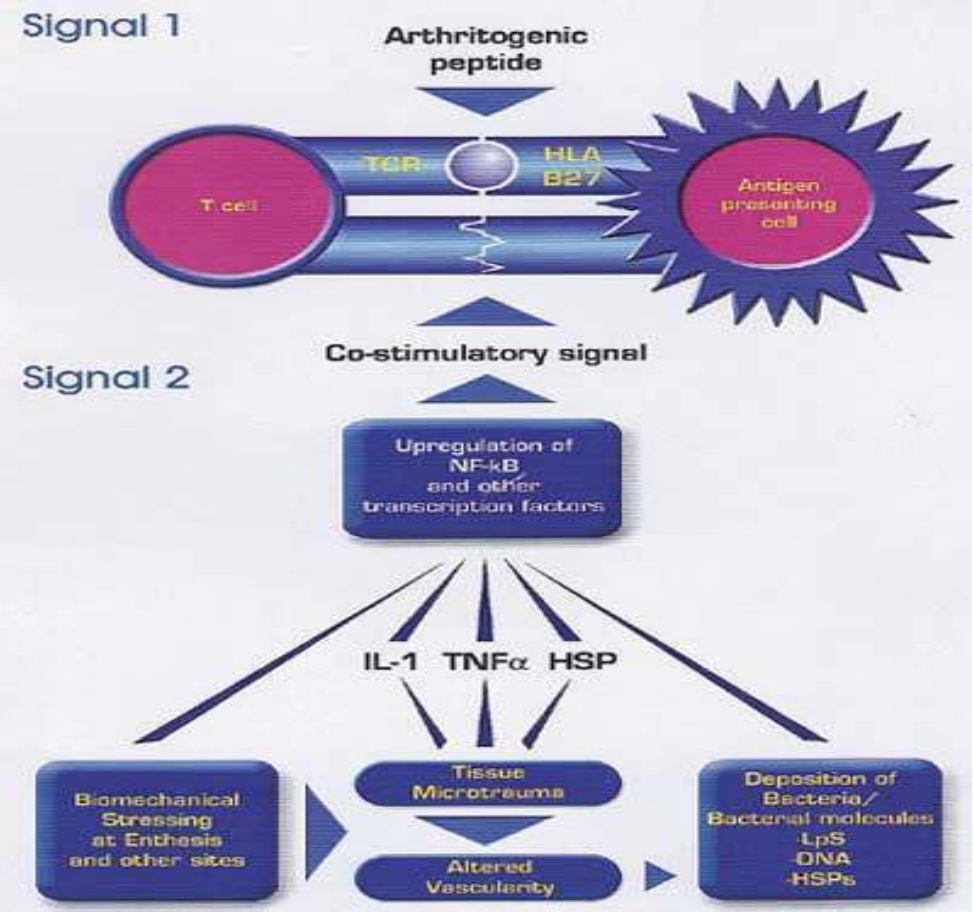
Figure :2



PATHOGENESIS

There are many theories regarding the pathogenesis of the disease and is mainly genetically inherited disease. The predominant genetic prediction is HLA-B27, it is MHC-class 1 molecule expressed in all cells, predominantly in antigen presenting cells and is coded by chromosome 6.This protein after tertiary folding binds with beta 2microglobin, loaded with oligopeptide and expressed in CD4 cells and NK cells[1].

Figure : 3



HLA-B27 also associated with other spondyloarthritislike reactive arthritis, psoriatic arthritis,and anterior uveitis[7] .There are about 25 allele in HLA-B27 and the most common subtype B*2705 and the other subtypes are 2701,2702,2704 and 2707.

Scofield and co-worker's suggested molecular mimicry LRRY LENG sequence Nona peptide which occurs both in HLA B27 andenterobacter.

Table : 1 Population/ disease entity and percentage of HLA-B27 positivity

POPULATION or DISEASE ENTITY	**HLA-B27 – POSITIVE**
Healthy whites	8%
Healthy African Americans	4%
Ankylosing spondylitis (whites)	92%
Ankylosing spondylitis (African Americans)	50%
Reactive arthritis	60-80%
Psoriasis associated with spondylitis	60%
IBD associated with spondylitis	60%
Isolated acute anterior uveitis	50%
Undifferentiated spondyloarthropathy	20-25%

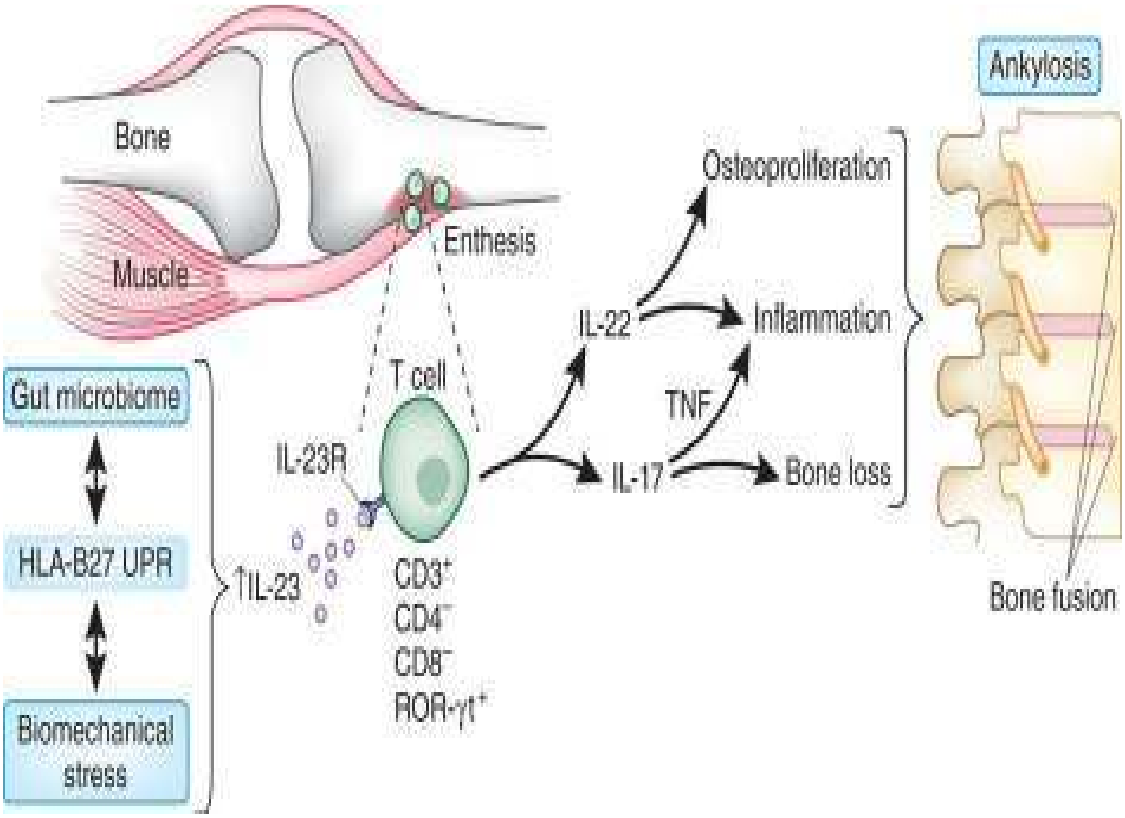
Another theory associated with this disease, immune response against G1 domain of specific antigen aggrecan which is large aggregating proteoglycan chondroitinsulfate present in intervertebral disc[7]. Normally this proteoglycan gives flexibility to the intervertebral disc and it is also present in anterior uveal tract, aorta, aortic valve.ARTS1[2] associated with the disease codes for endoplasmic reticulum aminopeptidasewhich cleaves cytokine receptor IL-6, TNF-A IL -1cleaved from cell surface important for antigen presentation by MHC-1.

Table : 2 Genes and its chromosome location.

Genes	**Chromosome Location**	**Gene Product/Function**
Definitely associated		
HLA-B27	6p21.3	Antigen presentation
IL-1 gene cluster	2q12.1	Modulator of inflammation
CYP 2D6	22q13.2	Metabolism of xenobiotics
ARTS1 (*ERAP1*)	5q15	ER aminopeptidase 1
IL23R	1p31.1	IL-23 receptor
Possibly associated		
ANKH	5p15	Ectopic mineralization
HLA-DRB1	6p21.3	Antigen presentation
Not associated		
TGF-ß, MMP3, IL-10, IL-6, Ig allotypes, *TCR, TLR4, NOD2/CARD15, CD14, NFßBIL1, PTPN22,* etc	Multiple	Multiple

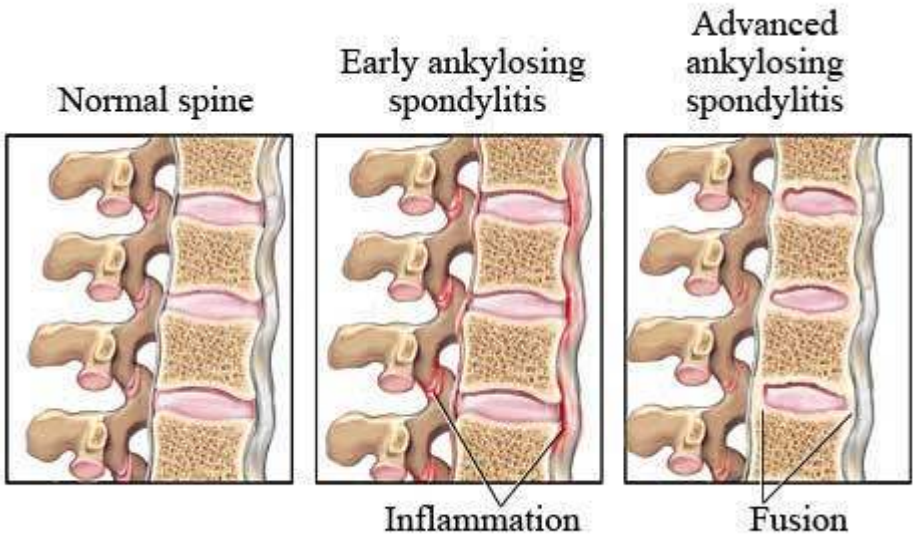
The primary pathology of the disease is chronical inflammation of the jointand also involving extra articular surfaces and the inflammatory cells are CD4+, CD8+T lymphocytes and macrophages[35,36]. Cytokines involved in this pathogenesis are tumour necrosis factor- alpha[3] and transforming growth factor –which are the key factors in the pathogenesis of the disease.

Figure : 4 Pathogenesis of AS



The early process is the formation of sub chondral granulation formation which erodes the normal joint. This is replaced by fibro cartilage and then ossification leading to new bone formation .This pathological process mainly occurs mainly in the ligamentous and capsular attachment site to bone which iscalled enthesitis[8]. Enthesitis is the hallmark of ankylosing spondylitis.

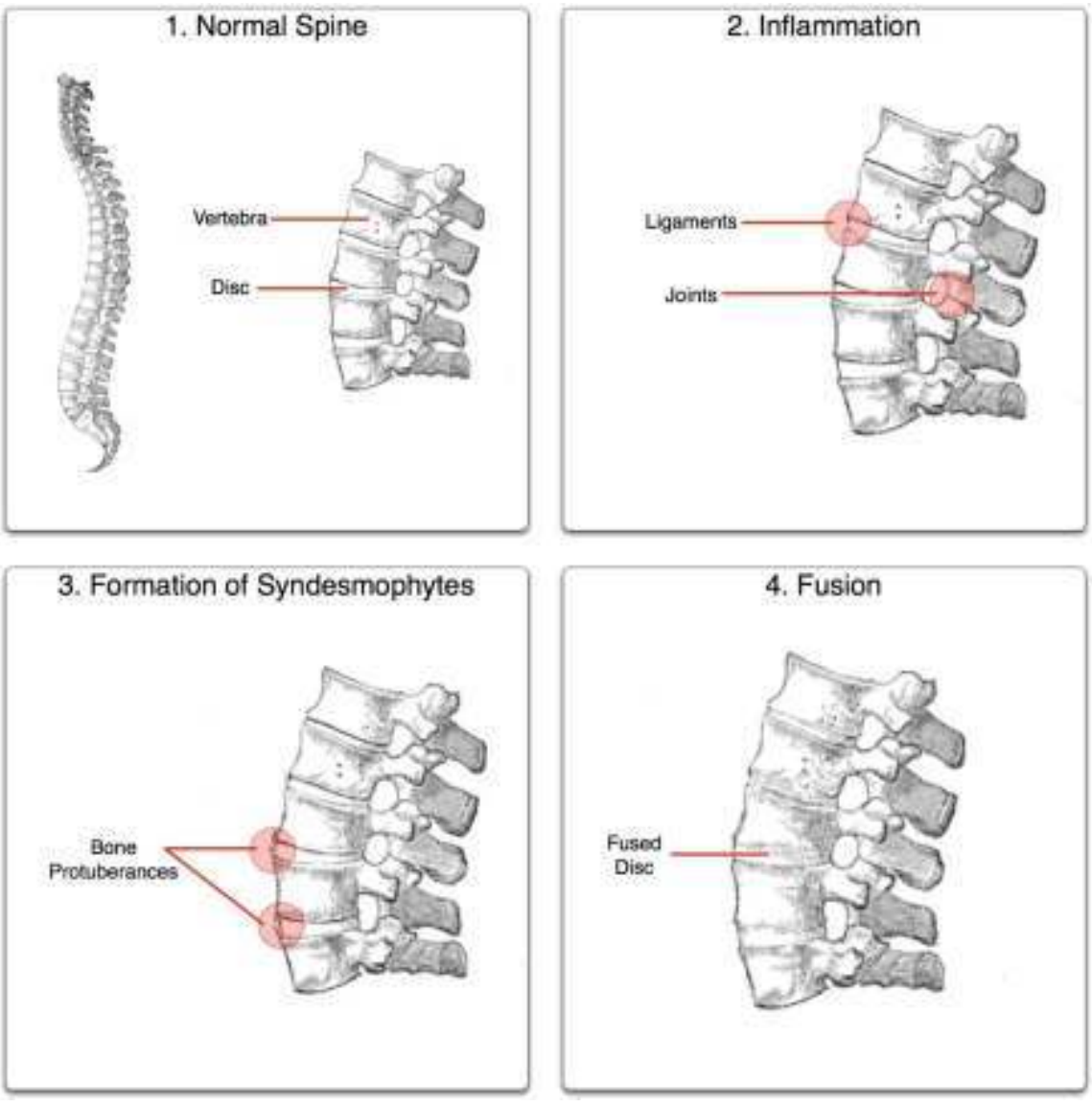
Figure :5



The disease progress from ligamental attachment site to the whole articular or joint space leading to new cartilage formation and bone formation and this leads to fusion of the joint.This leads to stiffness and immobility of the joint the typical ankylosis of the joint, characteristic symptom[8].

Initially sacroiliac joint is involved in ankylosing spondylitis and later involves the disc vertebral, apophyseal, costovertebral, costo – tranverse joints and paravertebral ligaments[9].

Figure :6stages of ankylosing spondylitis.



In the spine, it causes inflammation in the junction of vertebrae and the annulus fibrosis of the intervertebral disc space[9] .Ossification of the outer fibers of the disc causessyndesmophytes leading to bamboo appearance.

CLINICAL FEATURES

The start of the disease is usually insidious and the symptoms usually noticed in late adolescence or early adult. Males are twice commonly as compared to females and the age group is between 24 to 26 years[9]. The incidence of the disease is rare after 40 years about 5% and it is15% after 16 years, but may be high as 40% in developing countries.

The clinical manifestation shows features of both musculoskeletal and extraskeletalmanifestations.Chronic pain which is usually dull pain,felt deep in lumbar or gluteal region and stiffness for at least for a duration of about 3 months.Pain which is unilateral in one gluteal region and later becomes bilateral. More than 70% report daily pain and stiffness[8]. Initially,it's a nocturnal, intermittent pain and later it is persistent and stiffness improves with activity.

Fatigue is another common symptom which is presenting 60% of people and stiffness follows it. Increased fatigability is associated with increased pain and stiffness and reduced functional capacity.

Some complain of radiation of pain down the upper part of the posterior thigh region, which can be misdiagnosed as 'lumbago' or 'sciatica,' although neurologic examination is within normal limits[3,4,8]. These patients are mostly misdiagnosed as fibromyalgia.

Occasionally, back pain may be absent or too mild to impel the patient to seek medical care. .The symptoms may worsen after prolonged period of inactivity which is called gel phenomenon[8,9] .Pain improves withpnysicalactivity and worsen at night and early morning and also with exposure to cold.

Sometimes the pain starts in thecervical or in the thoracic region or anterior chest wall rather low back ache.

Joint involvement most commonly occur in the hips, shoulders, knee, wrist and toes. Peripheral joint involvement (shoulder and hip joint)is common in juvenile ankylosing spondylitis rather in adult age group[11].

The clinical examination usually parallels the inflammatory process. The most specific findings are limitation of movements due to loss of spinal mobility. There will be anterior, lateral and extension limitation of movement in the spine.Movement disorder is due to muscle spasm and bony ankyloses.

Limitation with movements or pain with motion of the joints is usually present. In the early course of the disease, symptoms are subtle and the physical examination may completely normal[8,9].Tenderness of the sacroiliac joint is more common. Another clinical finding is palpation of bony tenderness spots.

The range of movements can be assessed using modified schober test and this is not specific for ankylosing spondylitis. This test measures the lumbar spine flexion. Patient is asked to stand erectwith heel together and the marks are made in the lumbosacral junction, that's is at the midpoint of posterior superior iliac spine ,another at 5cm below and 10 cm above that point. Then the patient is asked to bent forward maximally without flexing the kneeand the distance between the two points is measured. If the distance is less than 4cm there will be decreased mobility and if greater than 5cmit is normal[1].

In case of thoracic spine involvement, its limitation can be measured as the difference between the maximal inspiration and maximal forced expiration in the fourth intercostal space. Normal chest expansion is more than 5cm[13,15].

Peripheral Enthesis and Joints

Peripheral enthesitis is identified by tenderness and swelling of ligamentous insertions and tendons. It occurs in approximately 33% of patients. The most common sites of enthesitis are the insertion of the Achilles tendon and plantar fasica on the calcaneus. Dactylitis (sausage digit)[8] is very uncommon in patient with ankylosing spondylitis.

Severe spinalankyloses and sacroiliac involvementand disease progression is more in male than in female[12,13]. In the cervical region, the atlantoaxial joint may be eroded due to the disease process causing ligament damage nerve compression, causing either root involvement or total nerve compression causing quadriparesis.Another major complication is the reduced bone density causing osteoporosis.

Osteoporosis in ankylosis spondylitis is more common in male than in female. Osteoporosis not only causes weakness and movement disability and is also prone for fractures even after minor trauma. Therefore, it is advisable to thoroughly investigate these individuals for fractures after minor trauma. Osteoporosis is more common in patients with syndesmophytes[8], cervical fusion and peripheral joint involvement. Apart from vertebral fractures, they are also prone for vertebral compression andassociated complications. The occurrence of the fractures depends on the disease duration.

Another spinal complication is non-infectious spondylodiscitis (Andersson lesion), which is about 8% of the diseased individual mostly in the lumbar and the thoracic region than in the cervical region[13]. Before concluding this diagnosis it is always advisable to rule out infections and trauma which is more common than this complication.

Fertility rate is not altered in female patients but the onset of disease and progression is increased during pregnancy and 6 months after delivery[16]. No antenatal and postnatal complications have been noted and there is no abnormal foetal outcomes like stillbirth, abortions in diseased pregnant females.

The clinical picture of the disease is extremely variable from nonspecific symptoms and to the extremely deformed spinal abnormality .Sometime the clinical examination and the investigations are within the normal limits in the initial phase.But if the disease has not been identified and not treated and this allows the inflammatory processes to progress, it leads to syndesmosis, joint fusion,immobility,leading to lumbar lordosis. Buttock atrophy and thoracic kyphosis.These deformities to occur a period of about 10 years is needed, resulting in stooped forward posture and difficulty in looking forward.

EXTRA ARTICULAR MANIFESTATION

Extra- articular manifestations can occur during the course of the disease or even before the typical manifestation of the disease. Since, it is a systemic disease it presents with nonspecific symptoms like fatigue, low back ache and myalgia.

The manifestations include ocular, gastrointestinal, cardiovascular, pulmonary, neurological, renal and hormonal.

OCULAR MANIFESTATIONS

Uveitis is the common ocular manifestation which may be the early presenting symptom. Acute anterior uveitis occurs in 30-40% of all the patients and is about 80-70% present in all HLA-B27 patients[17] .It occurs unilaterally, with recurrent episodes of blurring of vision ,pain and photophobia.

Most of the time the clinical symptoms and manifestations resolve spontaneously without any treatment. Sometimes it leads to loss of visionand this is due to accumulation of inflammatory cells in the anterior chamber and causing ocular and papillary dysfunction[33]. These leads to the occurrence of glaucoma and blurring of vision, all these complications eventually leads to loss of vision. Uveitis in reiter's disease is similar to ankylosing spondylitis, whereas in psoriatic

associatedarthropathyand inflammatory bowel disease is chronic and bilateral[11].

There are many treatment modalities for this complication like TNF-blocking agent or corticosteroids all these gives clinical improvement but does not prevent the recurrent episodes. The efficacy of the drug like etrnaceptib again controversial[23,24].Treatment does not guarantee the prognosis of the disease.

GASTROINTESTINAL MANIFESTATION

The gastrointestinal manifestation may be acute or chronic colitis. It is present asymptomatically in most of the patients, detected only in colonoscopy in the proximal ileum and colon but sometimes they will present with diarrhea.

Acute conditions clinically resemble common bacterial infections and the chronic conditions have symptoms mimicking inflammatory bowel disease. Usually chronic conditions present with the symptoms of diarrhea.

There is high incidence of AS occurrence in spondyloarthropathy. To the controversy is that the inflammatory bowel disease also has the articular manifestation like peripheral arthritis and sacrolitisasin ankylosing spondylitis with asymptomatic colitis[11].

Patients rarely develop crohn disease or ulcerative colitis. Retroperitoneal fibrosis is a rarely associated condition.

NEUROLOGICAL MANIFESTATION

Disease process causes fusion of vertebrae and new bone formation vulnerable for injury , leading to nerve compression ,damage resulting in neurological deficit .Cervical spine compression, dislocation and neurological deficit are common because of the vertebral fractures which occurs easily after minor trauma.

A rare complication of the disease cauda equine syndrome which slowly and progressively which was described by Browie and Haugh in 1961.It slowly starts with loss of sensation over the limbs and loss of rectal and urinary sphincter tone. Rare occurrence of dural sac, dural diverticula and arachanoiditis occurs[31].

Steroid therapy alone cannot improve the neurological conditions whereas surgical treatment is essential forduralectasia by laminectomy and lumboperitoneal shunting[29].

In some cases, dural calcification is also seen which improve the neurological conditions whereas surgical treatment is essential for dural ectasia by laminectomy andlumboperitoneal shunting

RENAL MANIFESTATION

The occurrence of renal abnormalities varies between 10-18% and the patients with this abnormalities have high ESR and raised CRP levels. Secondary amyloidosis is the most common manifestation ranging from 60% and other manifestations are as follows;

- Ig A nephropathy - 30%
- Mesangio proliferative glomerulonephritis - 5%
- Focal segmental glomerulosclerosis -1%
- Focal proliferative glomerulonephritis -1%.

Patients with high proteinuria and renal failure should be considered for renal amyloidosis .Renal amyloidosis is a rare complication. IgAnephropathy patients in ankylosing spondylitis are prone for renal failure. Multiple myeloma with raised IgA levels has also been reported.

CARDIOVASCULAR MANIFESTATION

Cardiac manifestations are found in 2-10% of ankylosing spondylitis patients[17]. The cardiovascular complications mainly occursin the late stages of the diseases. Not only aortitis, conduction defects valvularabnormalilities and cardiac myopathy are also associated with this disease.

The presence of aortic root and valve disease related to the duration of the disease and may predate the onset of any joint symptoms.Aortic insufficiency is due to the endarteritis leading to thickening involving aortic cusps and aorto-mitral junction[17,26]. The incidence of aortic insufficiency is about 1- 10%.Aortitisof the ascending aorta occurs due to the inflammation of the disease.

Conduction abnormalities are most common and predate other cardiac manifestations. Conduction abnormalities occur in this disease due to the inflammation of the interventricular septum and anomalies in the AV nodal artery leading to AV node dysfunction. The incidence of conduction block is 1- 33%. Conduction block is more common in HLA – positive patients. Implantation of pace maker in the case of complete heart block. The treatment for these patients is mostly surgical intervention.

Myocardial dysfunction seen in these patients is of diastolic varietyleading to left ventricular dysfunction and heart failure. Veryrarely pericarditis is seen in some patients.

There are high prevalence of ischemic heart disease in this disease for unknown reason. There has been research demonstrating significant

elevation of markers (i.e.,IL-6,CRP) accelerate risk of coronary heart disease[27].

PULMONARY MANIFESTATION

The pulmonary manifestations include fibrosis of the upper lobes, ventilator impairment due to chest wall restriction, interstitial lung disease spontaneous pneumothorax and sleep apnea. It usually occurs only in the late stages of the disease[17].

Apical fibrosis is a long recognized lung abnormality associated with the disease. Incidence is low ranging from 1.3%-30%[25] and associated with long duration of the disease. It may be unilateral or bilateral and followed by cystic changes to the lung.The apical lobe fibrosis which is detected in7% cases in routine chest x –ray.

The cause for fibrosis is unknown but recurrent aspiration leading to alteration in mechanical stress from a rigid thoracic spine, aspiration pneumonitis from defective ventilation and impaired cough secondary to alteration in respiratory mechanism has been proposed[16,26].

The appearance and distribution of the upper lobe abnormalities in ankylosing spondylitis led to the incorrect diagnosis of mycobacterium tuberculosis[20].

Ho et al study in Taiwan reviewed medical records of 2136 ankylosing spondylitis patients for infection revealed 2.9% with apical fibrosis and 65% with chronic infection from tuberculosis.

Hence, high index of suspicion and diagnostic evaluation for infection is required to differentiate between the two.

Interstitial lung disease (ILD) is a recognized feature of pulmonary involvement as a result of improved visualization of the lung parenchyma with HRCT. Fechner et al, in 1971 described diffuse bilateral interstitial and alveolar infiltrates involving the middle and the upper lung fields in a patient with long standing ankylosing spondylitis[13]. In addition to apical lobe fibrosis, restrictive lung functions and secondary lung infections in the bullae it also causes interstitial lung disease.

Several studies revealed the association between ILD and ankylosing spondylitis. Baser et al was first to report parenchymal changes in the early course of the disease in less than 5 years after the start of the disease.Casserly et al. study of HRCT in ankylosing spondylitis found interstitial lung disease in patients who did not reveal any abnormalitieswith chest x-ray but had abnormal pulmonary function testing.

Chest wall restriction and ventilator abnormalities

The chest wall restriction is due to the inflammation of the bony part, the joint .It causes edema,fusion of the joints spine and leading to restrictive chest wall function[16,18].Dorsal kyphosis due to thoracic spine involvement, costoverterbral, sternoclavicular, and sternomanubrial joints leading to impairment of expansion of the chest wall[16].

The pulmonary function done early in the diseased people detects the early impairment. Severe impairment of thechest wall movement causing restrictive lung functions.

Maghraoui et al. Study revealed statistically significant correlation between the disease activity and the pulmonary function test abnormalities. Pulmonary function testing showed predominant restrictive pattern abnormality in various studies.

Spontaneous pneumothorax

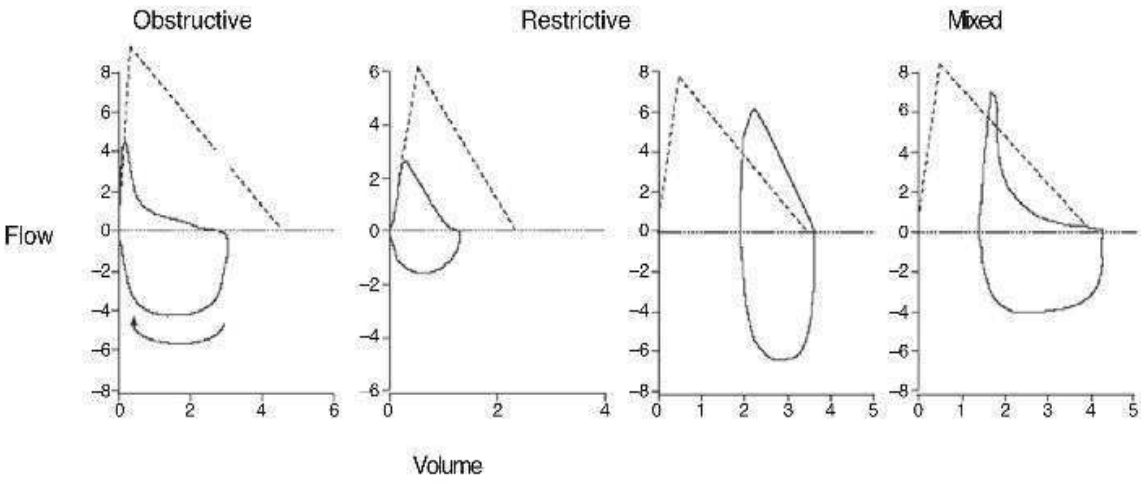
Spontaneous pneumothorax, a very rare complication of ankylosing spondylitis with an incidence of 0.29%. Apical lung abnormalities proposed to be primary risk factor for spontaneous pneumothorax in ankylosing spondylitis patient. The contribution of smoking being the risk factor for spontaneous pneumothorax in ankylosing spondylitis patients is unclear.

Sleep apnea

An increased incidence of sleep apnea found in patients with ankylosing spondylitis. Restriction of the oropharyngeal airway by compression from the cervical spine and restrictive pulmonary disease are possible mechanism for obstructive sleep apnea[17].

Frequency of pulmonary involvement varies depending on the diagnostic methods used. Pulmonary function test is done by using spirometry. Spirometry assess the mechanical function of the lung, respiratory muscle function, and the chest wall strength by measuring the lung volumes.

Figure : 7 Graphic display of flow versus volume.



There are different types of spirometers like volume displacement and flow –sensing spirometers.

INDICATIONS

- Evaluation of cases with respiratory symptoms .
- To assess the severity of the respiratory disease.
- To evaluate the response of the disease to treatment.
- To the evaluate the lung function before surgery for anaesthestic fitness.
- To assess the lung function to detect earlier the pulmonary abnormality in occupational exposures in industries to identify the occupational lung disease like bagassosis,byssinosis etc.

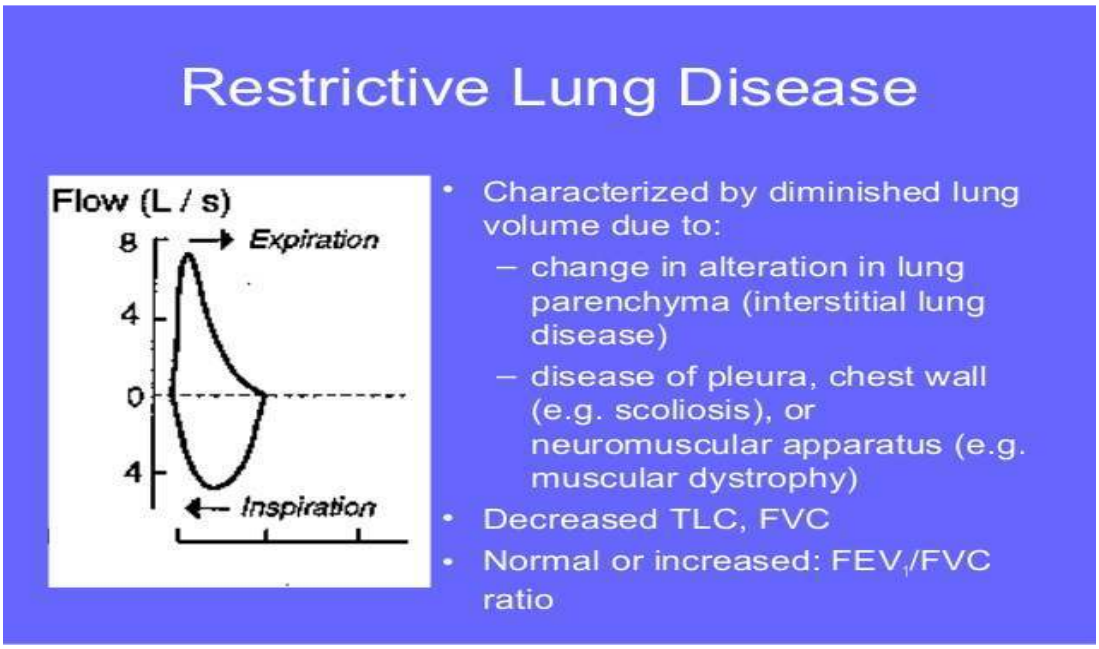
Table : 3 Alterations in ventilatory function.

	TLC	RV	VC	FEV_1/VC	MIP
Obstructive	N to ↑	↑	↓ or N	↓	N
Restrictive					
Pulmonary parenchymal	↓	↓	↓	N to ↑	N
Extraparenchymal					
Neuromuscular weakness	↓	Variable[a]	↓	Variable[a]	↓
Chest wall deformity	↓	Variable[b]	↓	N	N

The restrictive pattern of pulmonary disorder seen in AS patients mainly due to increased stiffness and ankylosing of the spine and

costoverbetral joints contribute to reduced spinal mobility and chest expansion[14,15].

Figure : 8 Restrictive pattern graph.



A characteristic pattern of restrictive abnormality in ILDs is preservation of flow rates resulting in the FV loop seen as a "narrow but tall" graph whereas in other types of restrictive abnormalities, reduction of FVC and FV loop is seen as a "normal shaped, miniature graph".

Patients with reduced spinal mobility should be subjected to pulmonary function test and relevant follow –up treatment. Hence, the association of musculoskeletal limitations and restrictive pattern in PFT mandates the importance of maintaining spinal flexibility in the management of AS[18].

CONTRAINDICATION

- It should not be done within 1 month of onset of myocardial infarction.
- Pain of any type abdominal or chest.
- Psychiatric patients or dementia or in confused state.
- Stress incontinence patients.
- Oral dentures or patients without teeth or facial pain.
- Pulmonary function testing revealed restrictive pattern of lung abnormality but an obstructive pattern was not observed in any patients.

LABORATORY FINDING AND IMAGING

The routine investigations done in this patients shows only mild changes like anemia of chronic disease which is present in 15% of diseased person The disease activity correlates with correlates with the CRP and ESR levels . Both the values are elevated in 75 % of cases. It can be used as marker of response to treatment and disease activity.

Serum IgA level is increased as it is acute phase reactant and also in renal manifestation as in IgA nephropathy. Acute phase reactant is increased mostly in extra spinal manifestation.

Ossification activity is denoted by increased by alkaline phosphatase which is present in 50% of cases. Creatinine kinase is also elevated in some cases. Platelet count is decreased in some cases.

HLA –B27 antigen is increased in ninety two percent of patients and it may be decreased in some ethnic backgrounds. As such it does not confirm the diagnosis but it can add features in addition to the clinical features and radiological features.

In addition to the ankylosing spondylitis it is increased in seronegative spondyloarthropathy, reactive arthritis, psoriatic arthritis, anterior uveitis and ulcerative colitis associated arthritis[11]. Antigen is present in varied prevalence in different population.

RADIOGRAPHIC FINDINGS

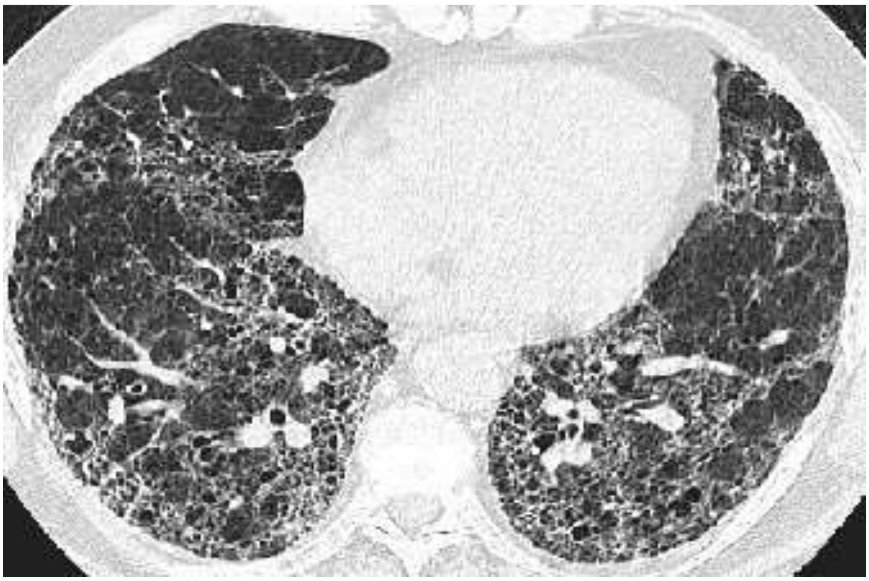
The involvement of sacroiliac joint is the commonest radiological evidence. The radiological signs include squaring of the vertebral bodies, sclerosing, erosion and newboneformation.Peripheral joint is also involved in this disease leading to narrowing of joint spaces, cystic changes, oedema and fibrosis of the joint. MRI and CT scan detects the early signs of the disease.

Figure : 9 Bamboo spine

HRCT in pulmonary evaluation of ankylosing spondylitis patients allows to identify that lung parenchymal changes occur earlier and extensive than accepted. With the development of HRCT, incidence of pulmonary involvement has changed a lot.

The characteristics pattern seen in UIP are coarse recticular or linear, honeycomb opacities and these features have a distinct predilection for peripheral, basal and subplerual regions of the lung[22].The Salient HRCT features of UIP that allows a confident diagnosis without resorting to surgical lung biopsy.

Figure : 10 HRCT picture of usual interstitial pneumonia.



DIAGNOSIS

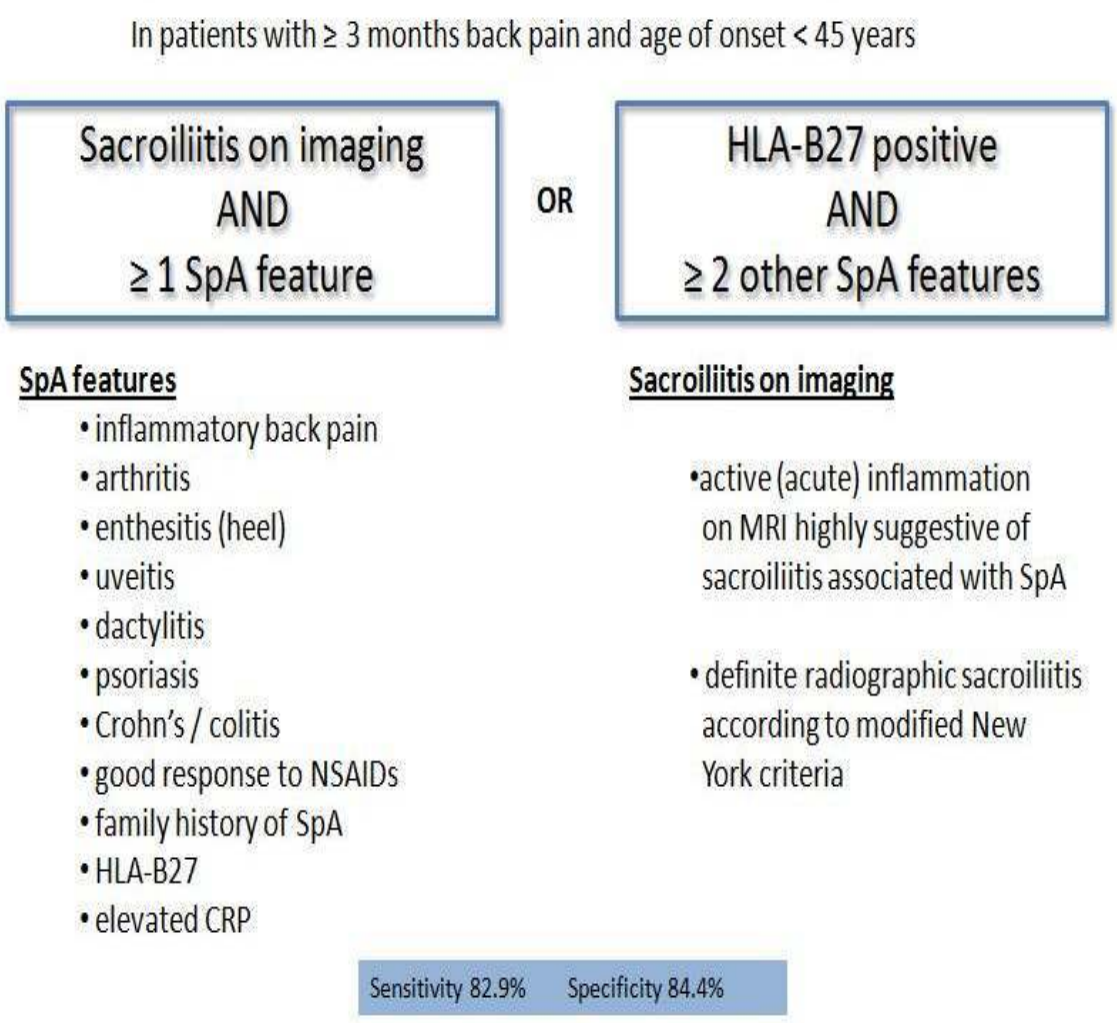
Ankylosing spondylitis can be difficult to diagnosis because the condition develops slowly and the clinical diagnosis requires expertise,there is no definitive test to confirm the diagnosis. But it is very important to diagnosis the disease early before the development of irreversible deformities.

The modified New York criteria(1984) was based on the presence of definite radiological sacroiliitis and that was too insensitive in mild or early cases.

New criteria for axial spondyloarthritis were propsed in 2009 by the assessment of Spodyloarthritis International Society (ASAS)[32].

The Assessment of SpondyloArthritis International Society (ASAS) has developed criteria for the classification of axial and peripheral SpA. These criteria incorporate the emerging concept of non radiographic axial SpA[42], but lack the radiographic damage to the sacroiliac joints needed to meet the modified New York criteria.

Table :4ASAS CRITERIA FOR AXIAL SPONDYLOARTHRITIS



DIFFERENTIAL DIAGNOSIS FOR ANKYLOSING SPONDYLITIS

- Mechanical back pain
- Inflammatory conditions – rheumatoid arthritis, psoriatic arthritis, reactive arthritis, Reiter's syndrome.
- Degenerative conditions – osteoarthritis.
- Infection – tuberculosis.
- Neoplasm, primary or secondary.
- Congenital spinal deformity
- Trauma
- Referred pain

Detailed history, clinical examination and appropriate lab investigations help in distinguishing these diagnoses from ankylosing spondylitis.

MANAGEMENT OF ANKYLOSING SPONDYLITIS

AS is a chronic condition for which there is no cure currently. The aim of treatment is mainly symptomatic with good control of symptoms, maintenance of function facilitated by early diagnosis and management of complications.

NON – PHARMACOLOGICAL MEASURES

All management of AS include exercise program and postural training designed to maintain posture and range of motion. In severe cases, intensive rehabilitation may be required. Spinal extension and deep-breathing exercises helps to maintain spinal mobility, promote chest expansion and erect posture. Swimming and hydrotherapy are help to maintain mobility and fitness. Maintaining an erect posture during day today activities and sleeping on affirm mattress tends to reduce the tendency towards thoracic kyphosis.

PHARMACOLOGICAL MEASURES

NSAIDS are the first line of pharmacological therapy for AS. These agents improve the symptoms by reducing the pain and decreasing the inflammation. Daily NSAIDS therapy slows radiographic progression.

TNF-alpha antagonists shown to be beneficial in the treatment of AS. Patient with long standing disease and complete spinal ankyloses shown significant reduction in the MRI inflammatory activity[28,29,30]. Etanercept, infliximab,golimumumab,adalimumab and certolizumabpego have all been as therapies for AS[23,24].

Other agents include corticosteroids, methotrexate, azathioprine; cyclophosphamide and cyclosporine are also beneficial in AS.

EVALUATION OF DISEASE ACTIVITY AND TREATMENT RESPONSE

Laboratory values including ESR and the C- reactive protein levels are commonly used to monitor the progression of the disease.

The European League Against Rheumatism (EULAR) recommend the radiographic evaluation of the sacroiliac joint and spine, helps for long-term monitoring of structural damage particularly new bone formation[30,37]. Short tau inversion recovery (STIR) sequences are sufficient to detect inflammation.

Numerous tools have been developed to measure AS disease activity in clinical trials are,

- Bath ankylosing spondylitis disease activity index (BASDAI)
- Bath ankylosing spondylitis functional index (BASFI)
- Bath ankylosing spondylitis metrology index (BASMI)
- Assessment in ankylosing spondylitis (ASAS)

The ASAS response criteria used to assess improvement in AS in clinical trials. The four domains are as follows:

- Patient global assessment of disease activity for the past week
- Patient assessment of back over the past week
- Function (BASFI)
- Inflammation (severity and duration of morning stiffness)

DISEASE OUTCOME

Disease usually have a favorable outcome, but one third of them develop disabling deformities. Predictors of severe AS outcome are

- Hip arthritis
- Increased ESR levels (>30mm/hr)
- Peripheral arthritis
- Juvenile onset (< 16 years)

The relationship of HLA-B27 positivity with severity of AS is less obvious compared to HLA-B27 negative individuals.

The rate of progression of the disease appears to be constant during several decades of the disease. Since disease occur at a younger age, socioeconomic consequences are higher[31].The stage of the disease and the delay of the treatment also influence the outcome of the disease.

SURGICAL CORRECTION AND STABILIZATION

- Vertebral osteotomy may benefit in patients with significiant impairment in line of sight, eating, and psychosocial well – being.
- Fracture stabilization in patients with advanced disease.
- Patient with significant involvement of the hips may benefit from total hip arthroplasty.

MATERIALS & METHODS

This study was conducted in Coimbatore medical college hospital, Coimbatore from July 2014 to July 2015. Patient attending the out patient department (OPD) in medical and rheumatology were selected as case and control group in this study. The study was approved by the Institute's ethics committee.

PATIENTS

This study was conducted in 50 cases of ankylosing spondylitis patients attending the medical and rheumatology OPD.

SELECTION CRITERIA

Inclusion Criteria

- Adult patients (both sex) between the age group of 18 to 60
- Patients satisfying Assessment of Ankylosing Spondylitis International Society (ASAS) criteria for Ankylosing Spondylitis criteria

Exclusion Criteria

- Pregnant women
- Minors (below the age of consent)
- Persons suffering from other interstitial lung disease
- Persons suffering from pulmonary TB
- Persons suffering from other obstructive and restrictive lung diseases
- Persons suffering from pleural diseases
- Persons suffering from Psoriatic Arthritis
- Persons not capable of giving consent (psychiatric patients)
- Persons unwilling to undergo the study (who refused to consent)

ASAS CRITERIA FOR ANKYLOSING SPONDYLITIS

Applied to persons of chronic low back ache for >3 months and age <45 years

Person should satisfy Either 1 imaging and 1 clinical parameter Or Positive HLA B27 test and 2 clinical parameters

Imaging Parameters:

1.X-ray finding of Sacroiliitis at grade 2 bilateral or grade 3 or 4 unilateral(according to modified New York Criteria 1984)

(OR)

2.Active inflammation of sacro iliac joints on MRI

Clinical Parameters:

1.Arthritis

2.Enthesitis

3.Uveitis

4.Psoriasis

5.Crohn’s disease and Ulcerative colitis

6.Good response to NSAID’S

7.Inflammatory back pain

8.Family history of SpondyloArthritis

9.Elevated C-Reactive Protein

METHODOLOGY

Study was conducted in 50 patients with ankylosing spondylitis attending medical and rheumatology OPD fitting ASAS criteria and the inclusion criteria. Patients who satisfy the inclusion and ASAS criteria were selected and informed consent obtained before the start of the study. Detailed history taking and clinical examination was performed in all the selected patients and also checked for the symptoms and signs of pulmonary manifestations. Laboratory investigations like complete haemogram, differential blood cell count,erythrocyte sedimentation rate(ESR),C-Reactive protein(CRP), renal function test, liver function test, serum lipid profile were performed.

Patients were futher subjected to other investigations like radiological imaging like chest x-ray and HRCT(high resolution computed tomography).

Patients were subjected to pulmonoary function test(PFT).

PULMONARY FUNCTION TEST

All patients were underwent a pulmonary function test, evaluated by means of a spirometer.It is very simple expression of the lung function, just like measuring blood pressure.It measures airflow during inspiration and expiration. The spirometeric measurements were

performed with the patients sitting in a upright position with a nose clip attached.

Activities that should be avoided prior to spirometry are consuming alcohol, vigorous exercise, tight clothes and a large meal.

Measurements included are

Vital Capacity: The recording of the expiratory flow of air from the fully inflated lung is called vital capacity manoeuvre.

FVC -Forced Vital capacity: the maximal amount of air exhaled from fully inflated lung is called forced vital capacity.

FEV1 - Forced Expiratory Volume:the amount of air exhaled in the first second of the vital capacity manoeuvre.

PEF – Peak Expiratory Flow: the maximal expiratory flow after a maximum lung inflation.

FEV1/FCV% - the absolute ratio derived from the observed values. Used in the diagnosis of obstructive ventilator diseases.

Based on the results obtained patients are categorized as restrictive ventilator pattern (FVC< 80%, FEV1/FVC > 70%, decreased or normal FEV1), obstructive ventilator pattern (FEV1/FVC <70%, decreased

FEV1, normal or decreased FVC) or normal pulmonary function(FVC > 80%, FEV1> 80%, FEV1/FVC > 80%)

FVC% predicted is used to determine the severity of restriction.

MILD: FVC% between 60 -80%.

MODERATE: FVC% between 45 - 60%.

SEVERE: FVC% less than 45%.

A characteristic pattern of restrictive abnormality in ILDs is preservation of flow rates resulting in the FV loop seen as a "narrow but tall" graph whereas in other types of restrictive abnormalities, reduction of FVCand FV loop is seen as a "normal shaped, miniature graph".

HIGH RESOLUTION COMPUTED TOMOGRAPHY

HRCT is the radiological imaging technique that closely reflects the changes in lung structure. It is the method for the diagnostic work-up of suspected or known ILD patients. HRCT provides a global assessment of anatomy of the lung. Therefore, this imaging technique improves the sensitivity and specificity of clinical and histopathological diagnosis. HRCT has the ability to detect discrete abnormalities as small as 0.3 mm and that allows more accurate diagnosis and optimal management.

Interstitial involvement is a commonest manifestation of ankylosing spondylitis. Usual interstitial pneumonia and honeycomb pattern are seen in interstitial lung disease.

STATISTICAL ANALYSIS

The data are reported as the mean +/- SD or the median , depending on their distribution. The difference in quantitative variables between groups were assessed by means of the un[aired t test. Comparsion between groups was made by the Non parameteric Mann – whitney test.

A Chi Square test was used to assess difference in categoric variables between groups.

A p valve of < 0.05 using a two-tailed test was taken as being of significance for all statistical tests. All data were analysed with statistical software package

RESULTS

A total of 50 patients diagnosed with ankylosing spondylitis based on ASAS Criteria were selected for evaluating the pulmonary manifestation in these patients from july 2014 to july 2015

Table : 5 AGE DISTRIBUTION OF THE STUDY POPULATION

AGE DISTRIBUTION

	GENDER			
AGE	MALE	FEMALE	TOTAL	(%)
31- 35	15	9	24	24%
36 – 40	41	11	52	52%
41 – 45	17	4	21	21%
> 45	3	0	3	3%
TOTAL	76	24	100	

The age of the study population ranged between 30- 60 years and 24 % of them were in the age group between 31- 35, 52 %were between 36- 40 and 3% were greater than 45 years.

FIGURE : 11 AGE DISTRIBUTION WITH GENDER

In the study population, 15% males and 9% females were in the age group of 31- 35, 41% males and 11% females in the age group of 36- 40, 17% males and 4% females between 41-45 years and 3% males were above 45 years of age.

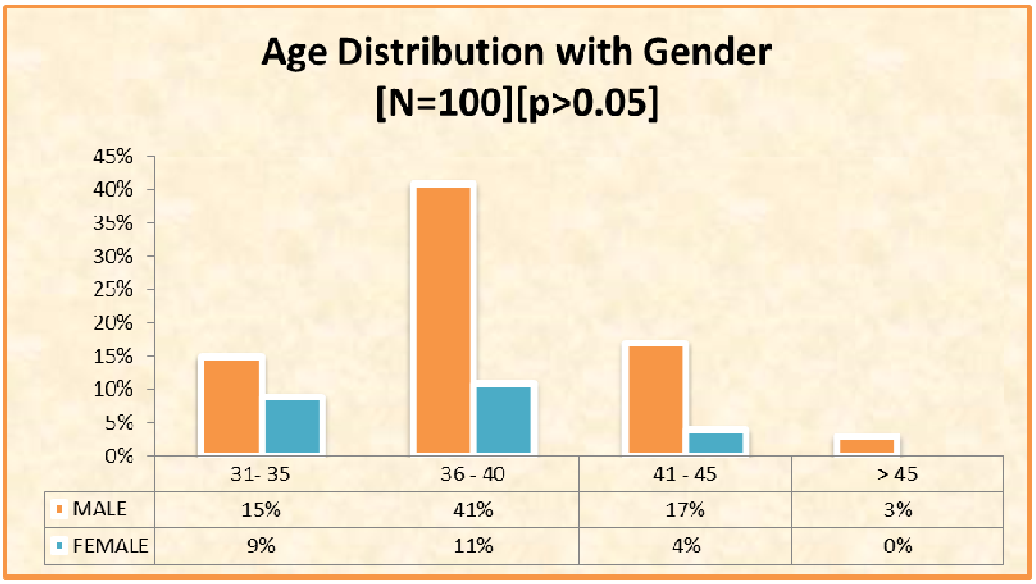
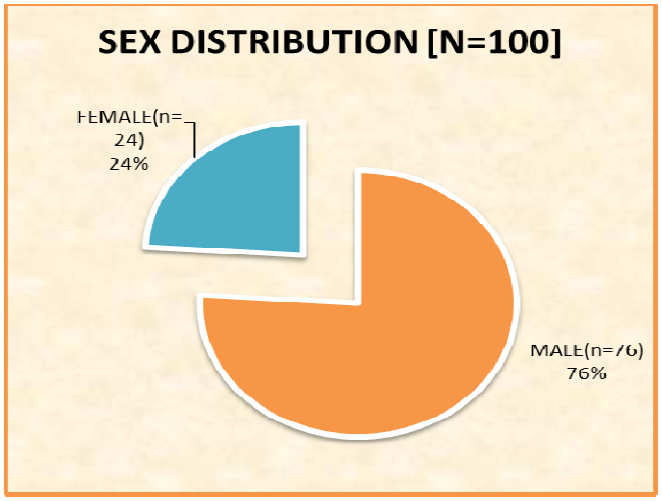


FIGURE : 12 SEX DISTRIBUTION



In the study population , 24% were females and 76% were found to be males.

TABLE:6 MEAN AGE WITH GENDER OF THE STUDY POPULATION

Mean Age with Gender							
Gender	Mean [Years]	SD	95% CI for Mean		Minimum	Maximum	Sig
			Lower	Upper			
MALE	38.63	3.413	37.85	39.41	32	46	
FEMALE	37.21	3.176	35.87	38.55	33	45	<0.05
Total	38.29	3.397	37.62	38.96	32	46	

The mean age of the males is 38.63 and for the female is 37.21 and the mean age with gender of the study group is 38.29 and its p value is<0.05 . Hence, there is a significant association was observed.

FIGURE :13 MEAN AGE WITH GENDER.

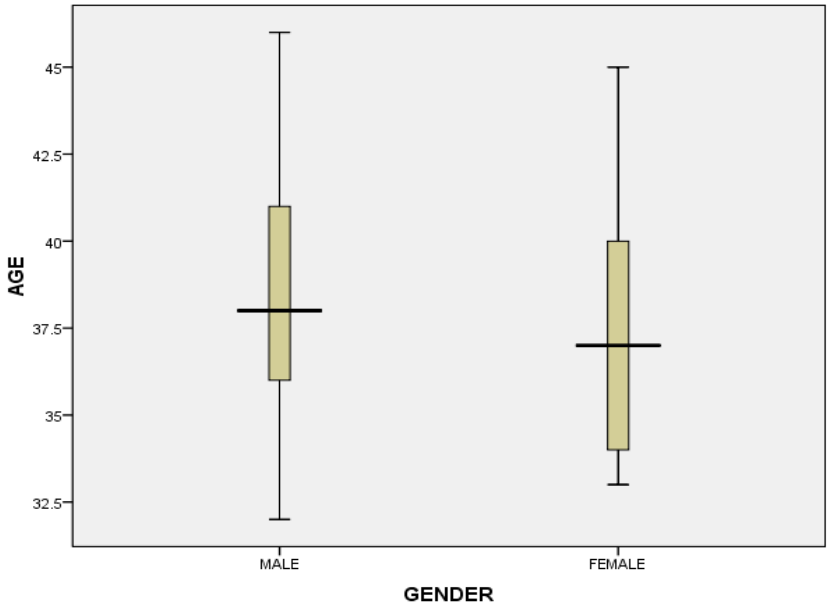


TABLE: 7AGE DISTRIBUTION IN STUDY GROUPS

There were about 50 people in the case and control group. Maximiumdistribution of cases were between 36 - 40 years of age.

AGE DISTRIBUTION IN STUDY GROUPS

	STUDYGROUP			
AGE	CASES	CONTROL	TOTAL	(%)
31- 35	12	12	24	24%
36 – 40	25	27	52	52%
41 – 45	13	8	21	21%
> 45	0	3	3	3%
TOTAL	50	50	100	

FIGURE :14 AGE DISTIBUTION

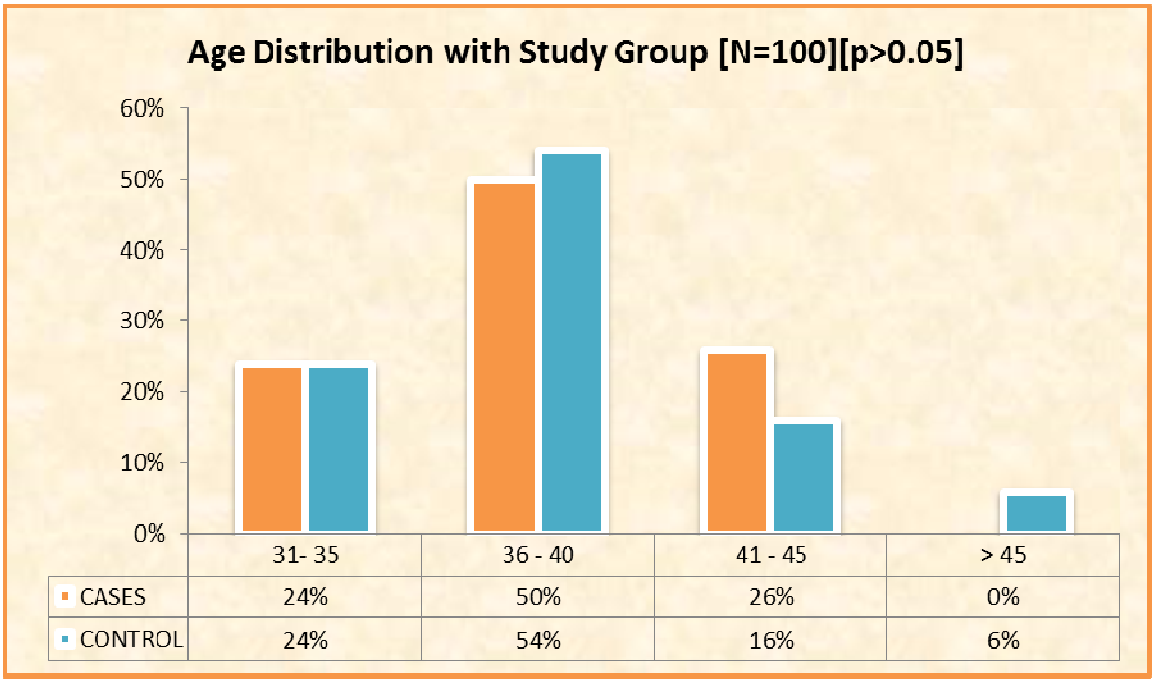


FIGURE : 15 DURATION OF DISEASE IN CASES

The number of cases in the duration < 5 years were 26 cases which is 52% ,5-10 years were 19 cases -38% and > 10 years is about 10%.

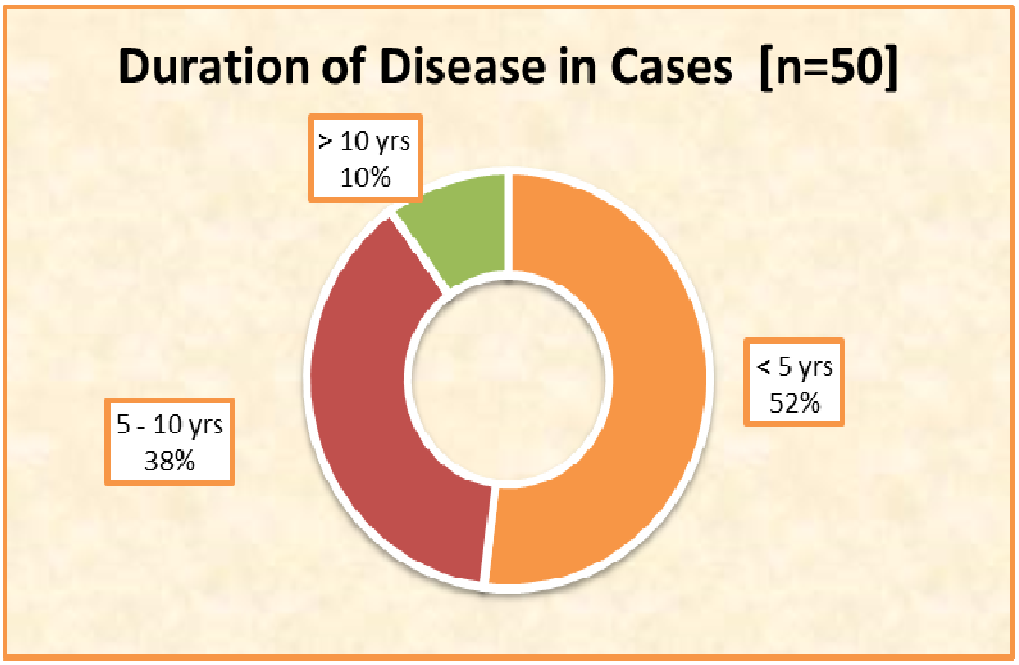


TABLE : 8 DURATION OF DISEASE

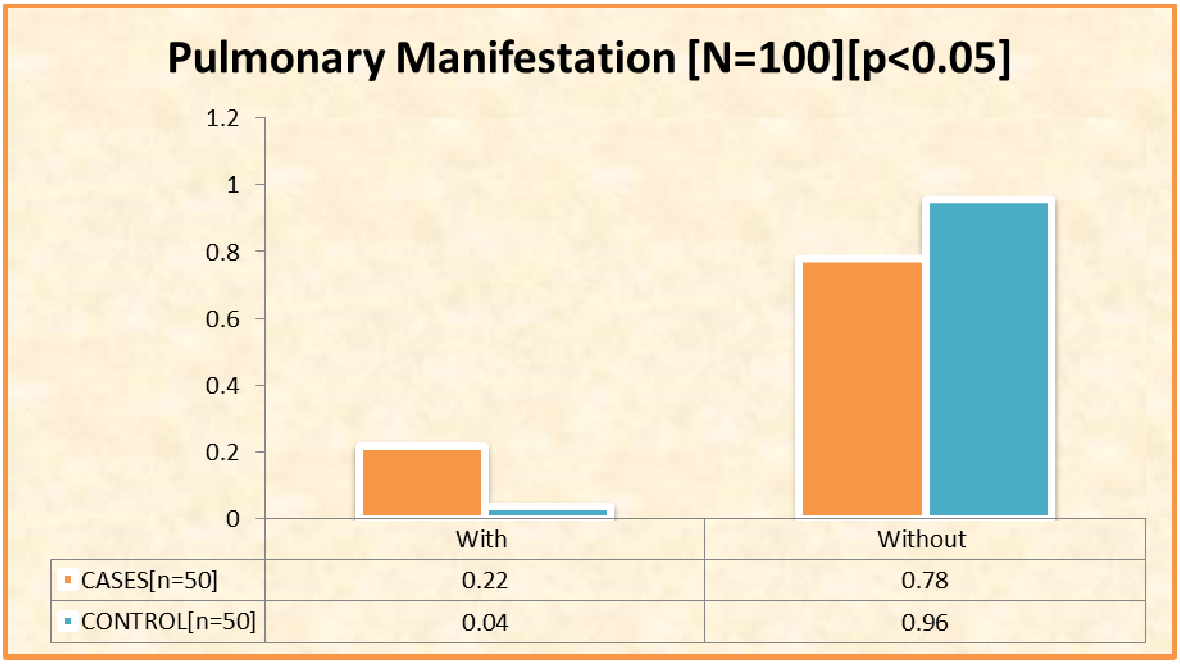
Duration of Disease in cases		
Duration	**n**	**(%)**
< 5 yrs	26	52%
5 - 10 yrs	19	38%
> 10 yrs	5	10%
Total	50	100%

TABLE:9PULMONARY MANIFESTATION IN THE STUDY POPULATION

Pulmonary Manifestations according to study group

Pulmonary manifestations	STUDYGROUP			
Manifestaton	CASES	CONTROL	TOTAL	(%)
With	10	1	11	11%
Without	40	49	89	89%
TOTAL	50	50	100	

FIGURE :16



The number of patients with pulmonary manifestation in the study population were 11 in which 11% of them with pulmonary manifestation are from cases(AS) and 89% without manifestation are from control group.

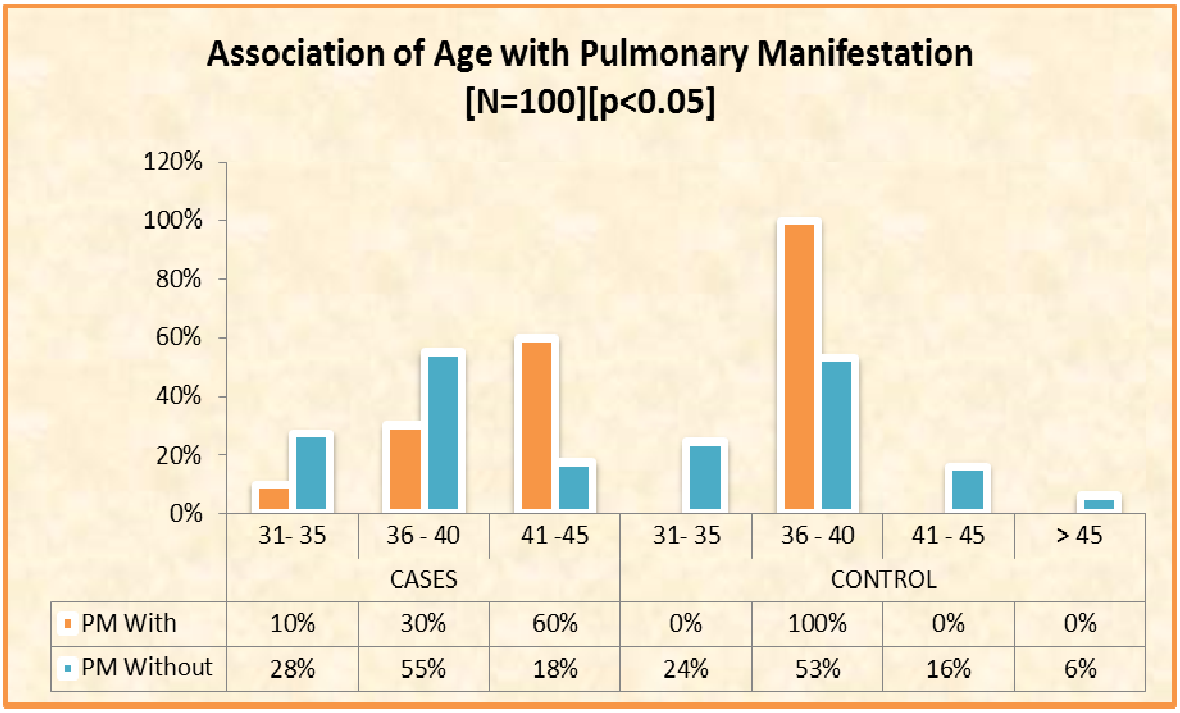
TABLE:10 ASSOCIATION OF AGE WITH PULMONARY MANIFESTATION

Association of Age with Pulmonary Manifestations in study Groups

STUDYGROUP	Age	Pulmonary Manifestations		Total	(%)	Sig
		With	Without			
CASES	31- 35	1	11	12	24%	<0.05
	36 – 40	3	22	25	50%	
	41 – 45	6	7	13	26%	
	Total	**10**	**40**	**50**	**100%**	
CONTROL	31- 35	0	12	12	24%	>0.05
	36 – 40	1	26	27	54%	
	41 – 45	0	8	8	16%	
	> 45	0	3	3	6%	
	Total	**1**	**49**	**50**	**100%**	

Significant association was observed in the occurrence of pulmonary manifestation in the age group between 31 – 45 years in patients with ankylosing spondylitis(P value < 0.05). In the control group, there was an insignificant association between age and pulmonary manifestation.

FIGURE:17 ASSOCIATION OF AGE WITH PULMONARY MANIFESTATION



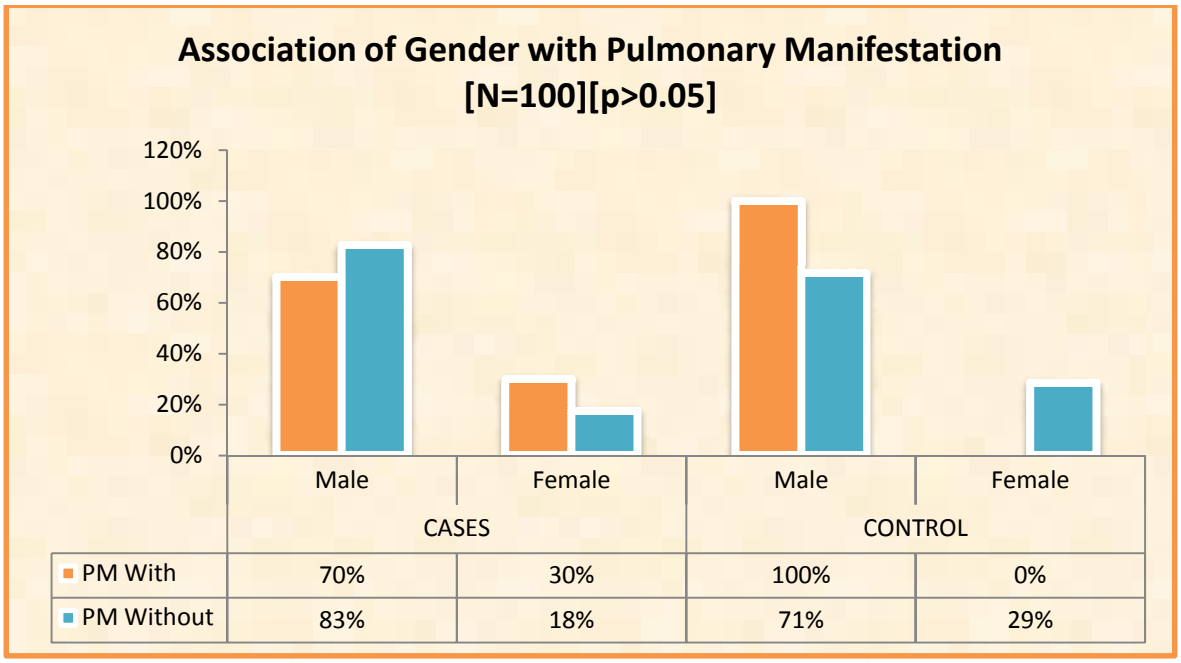
	CASES			CONTROL			
	31- 35	36 - 40	41 -45	31- 35	36 - 40	41 - 45	> 45
PM With	10%	30%	60%	0%	100%	0%	0%
PM Without	28%	55%	18%	24%	53%	16%	6%

TABLE:11 ASSOCIATION OF GENDER WITH PULMONARY MANIFESTATION IN THE STUDY GROUP

Association of Gender with Pulmonary Manifestations in study Groups

STUDYGROUP	Gender	Pulmonary Manifestations		Total	(%)	Sig
		With	Without			
CASES	Male	7	33	40	80%	
	Female	3	7	10	20%	>0.05
	Total	**10**	**40**	**50**	**100%**	
CONTROL	Male	1	35	36	72%	
	Female	0	14	14	28%	>0.05
	Total	**1**	**49**	**50**	**100%**	

FIGURE :18



Out of 10 cases with pulmonary manifestation 7 were males and 3 were females in the case group and in the control group 1 male patient is with pulmonary manifestation.

TABLE: 12 ASSOCIATION OF DURATION OF DISEASE WITH PULMONARY MANIFESTATION IN THE STUDY GROUP

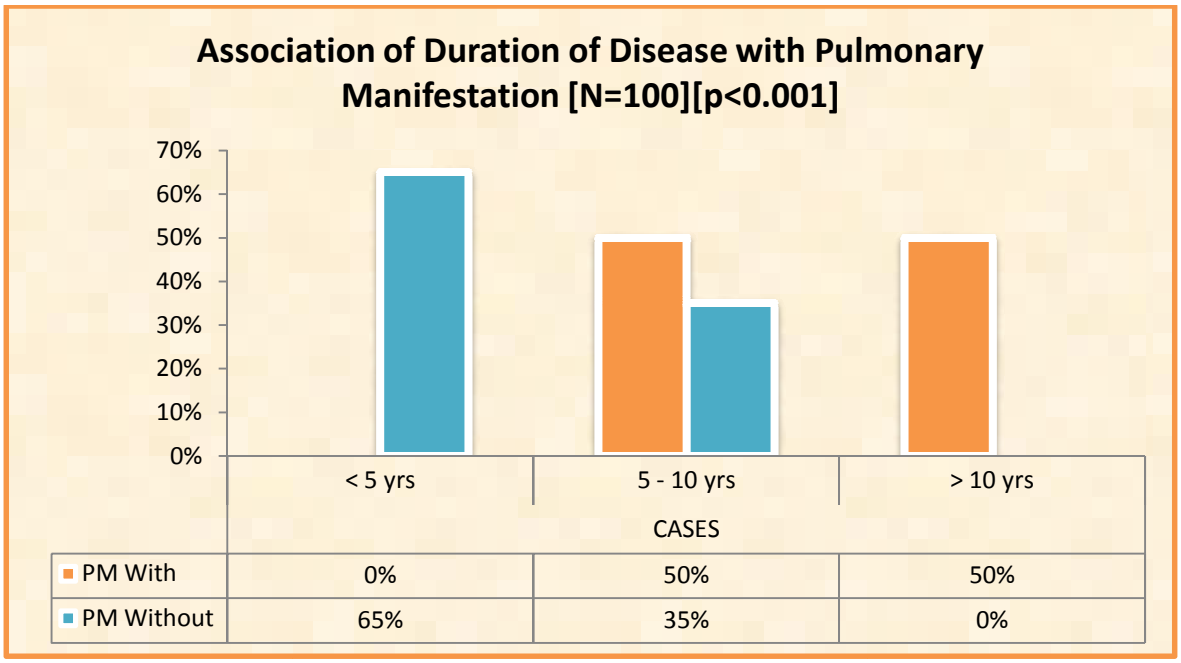
Association of Duration of Disease with Pulmonary Manifestations in study Groups

		Pulmonary Manifestations				
STUDYGROUP	**Duration**	**With**	**Without**	**Total**	**(%)**	**Sig**
CASES	< 5 yrs	0	26	26	52%	<0.001
	5 - 10 yrs	5	14	19	38%	
	> 10 yrs	5	0	5	10%	
	Total	**10**	**40**	**50**	**100%**	

Excellent significant association of duration of disease with pulmonary manifestation in patient with ankylosing spondylitis.

In the study population, increased chance of pulmonary manifestation with longer the duration of the disease. (ankylosing spondylitis)

FIGURE : 19 ASSOCIATION OF DURATION OF DISEASE WITH PULMONARY MANIFESTATION



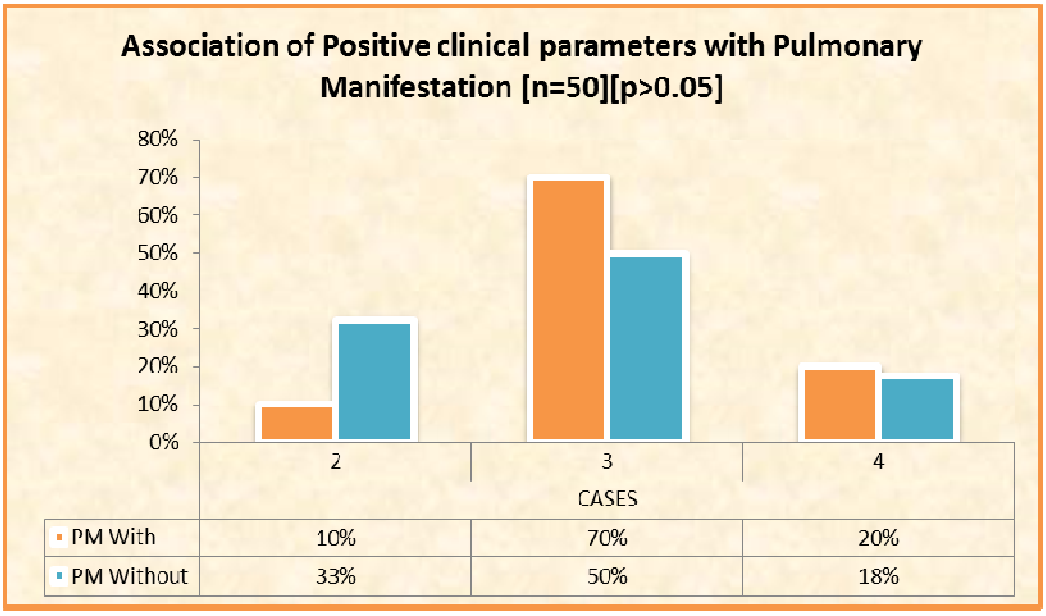
Pulmonary manifestations increases in patients with ankylosing spondylitis for a longer duration, hence the association of duration of the disease with pulmonary manifestation as a very significant p value of <0.001.

TABLE:13 ASSOCIATION OF POSITIVE CLINICAL PARAMETERS WITH PULMONARY MANIFESTATION IN STUDY GROUP

Association of Positive Clinical Parameters with Pulmonary Manifestations in study Groups

STUDYGROUP	No of clinical	Pulmonary Manifestations With	Without	Total	(%)	Sig
CASES	2	1	13	14	28%	>0.05
	3	7	20	27	54%	
	4	2	7	9	18%	
	Total	**10**	**40**	**50**	**100%**	

FIGURE :20



14 cases were associated with 2 positive clinical parameters out of which, 1is with pulmonary manifestation and 13 without the manifestation.27cases were with 3 clinical parameters 7 were with manifestation and 20 were without manifestation. 9 cases are with 4 clinical parameters 2 cases with manifestation and 7 without manifestation.

TABLE:14ASSOCIATION OF X-RAY IMAGING GRADE WITH PULMONARY MANIFESTATION IN STUDY GROUP

Association of X ray imaging grade with Pulmonary Manifestations in study Groups

STUDYGROUP	X ray Grading	Pulmonary Manifestations With	Without	Total	(%)	Sig
CASES	2 B/L	2	10	12	24%	>0.05
	3 U/L	5	15	20	40%	
	3 B/L	2	5	7	14%	
	4 U/L	0	9	9	18%	
	4 B/L	1	1	2	4%	
	Total	**10**	**40**	**50**	**100%**	

FIGURE: 21

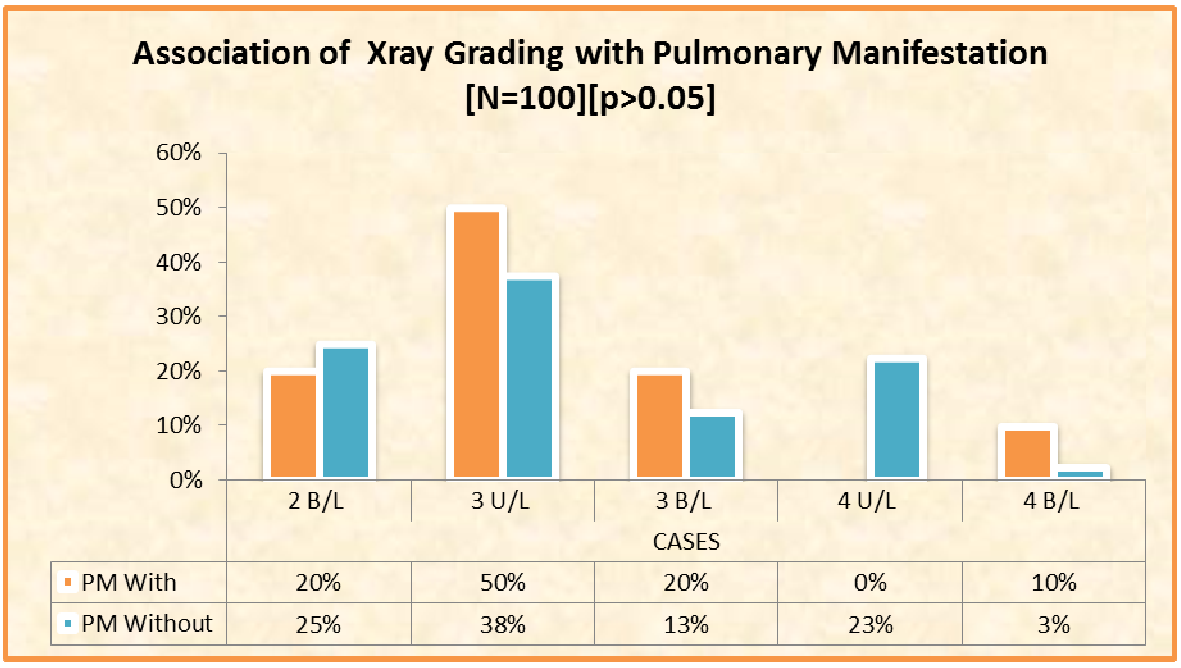
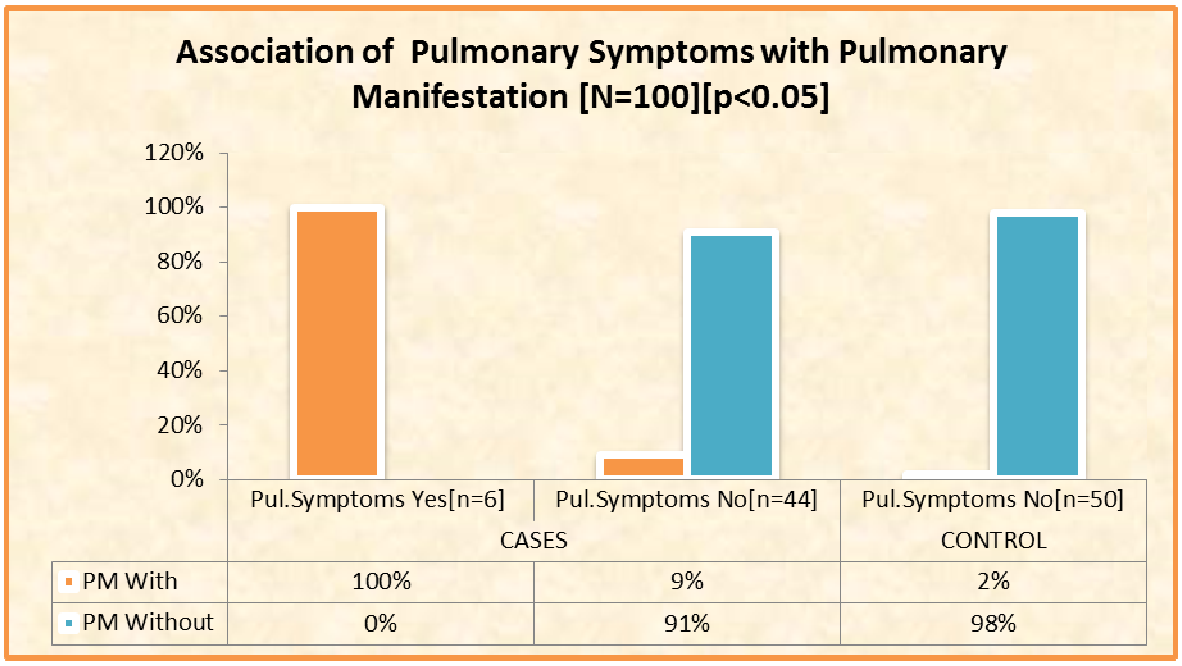


TABLE:14 ASSOCIATION OF PULMONARY SYMPTOMS WITH PULMONARY MANIFESTATION IN STUDY GROUPS

Association of Pulmonary Symptoms with Pulmonary Manifestations in study Groups

STUDYGROUP	Pulmonary Symptoms	Pulmonary Manifestations With	Without	Total	(%)	Sig
CASES	YES	6	0	6	12%	
	NO	4	40	44	88%	<0.05
	Total	**10**	**40**	**50**	**100%**	
CONTROL	NO	1	49	50	100%	
	Total	**1**	**49**	**50**	**100%**	

FIGURE: 22



Out of 50 ankylosing spondylitis patients, 10 patients were having pulmonary manifestation, out of which 6 were associated with pulmonary symptoms. Significiant association of pulmonary symptoms with pulmonary manifestation was observed in patients with ankylosing spondylitis with p value of <0.05.

TABLE:15 ASSOCIATION OF CHEST X-RAY WITH PULMONARY MANIFESTATIONS IN STUDY GROUPS

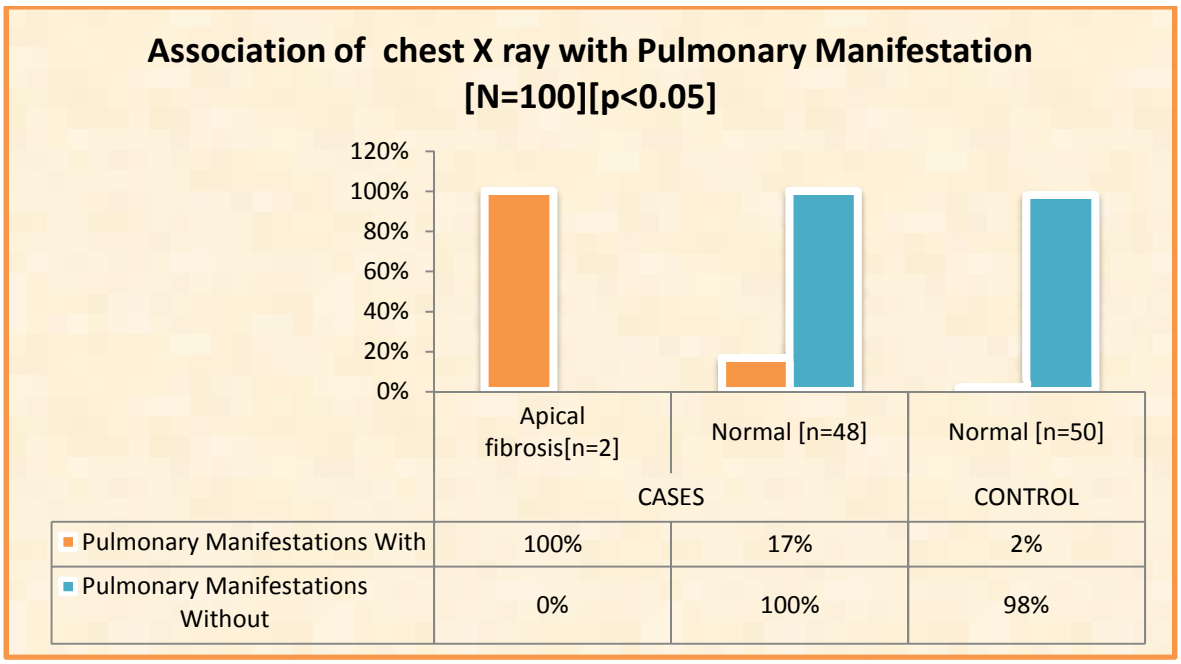
Association of Chest X ray with Pulmonary Manifestations in study Groups

STUDYGROUP	Chest X ray	Pulmonary Manifestations		Total	(%)	Sig
		With	Without			
CASES	Apical fibrosis	2	0	2	4%	
	Normal	8	40	48	96%	<0.05
	Total	**10**	**40**	**50**	**100%**	
CONTROL	Normal	1	49	50	100%	
	Total	**1**	**49**	**50**	**100%**	

Out of 10 patients with pulmonary manifestation, apical fibrosis seen in chest x-ray in 2 patients, hence a significant association apical fibrosis in patients with pulmonary manifestation was observed in ankylosing spondylitis patients.

(P value < 0.05)

FIGURE: 23 ASSOCIATION OF CHEST X-RAY WITH PULMONAY MANIFESTAION IN STUDY GROUP



Significant association of chest x-ray with pulmonary manifestation was observed in patients with ankylosing spondylitis.

TABLE:16 ASSOCIATION OF PFT WITH PULMONARY MANIFESTATIONS IN STUDY GROUP

Association of PFT with Pulmonary Manifestations in study Groups

STUDYGROUP	PFT	Pulmonary Manifestations		Total	(%)	Sig
		With	Without			
CASES	Mild	6	0	6	12%	<0.01
	Moderate	4	0	4	8%	
	Normal	0	40	40	80%	
	Total	**10**	**40**	**50**	**100%**	
CONTROL	Normal	1	49	50	100%	>0.05
	Total	**1**	**49**	**50**	**100%**	

Out of 50 ankylosing spondylitis patients, 10 were with pulmonary manifestation in which 6 patients had mild restriction and 4 patients with moderate restriction on pulmonary function testing and hence there is a signigificant association with P value < 0.05.

FIGURE: 24

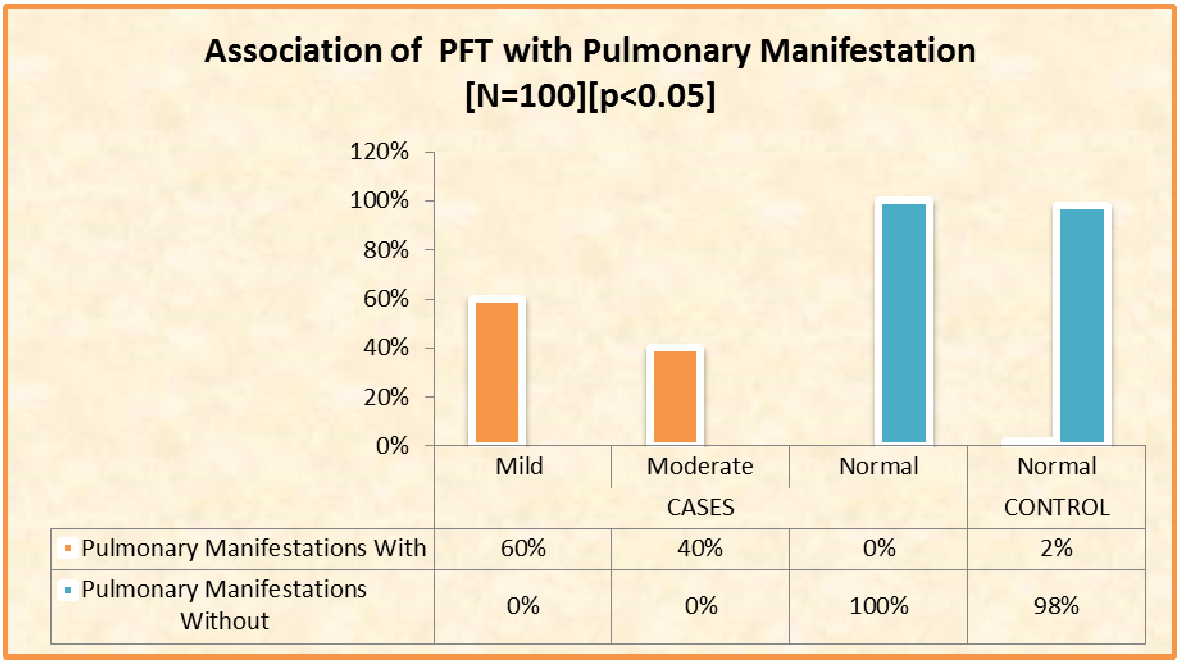


TABLE:17 ASSOCIATION OF HRCT WITH PULMONARY MANIFESTATIONS IN STUDY GROUPS

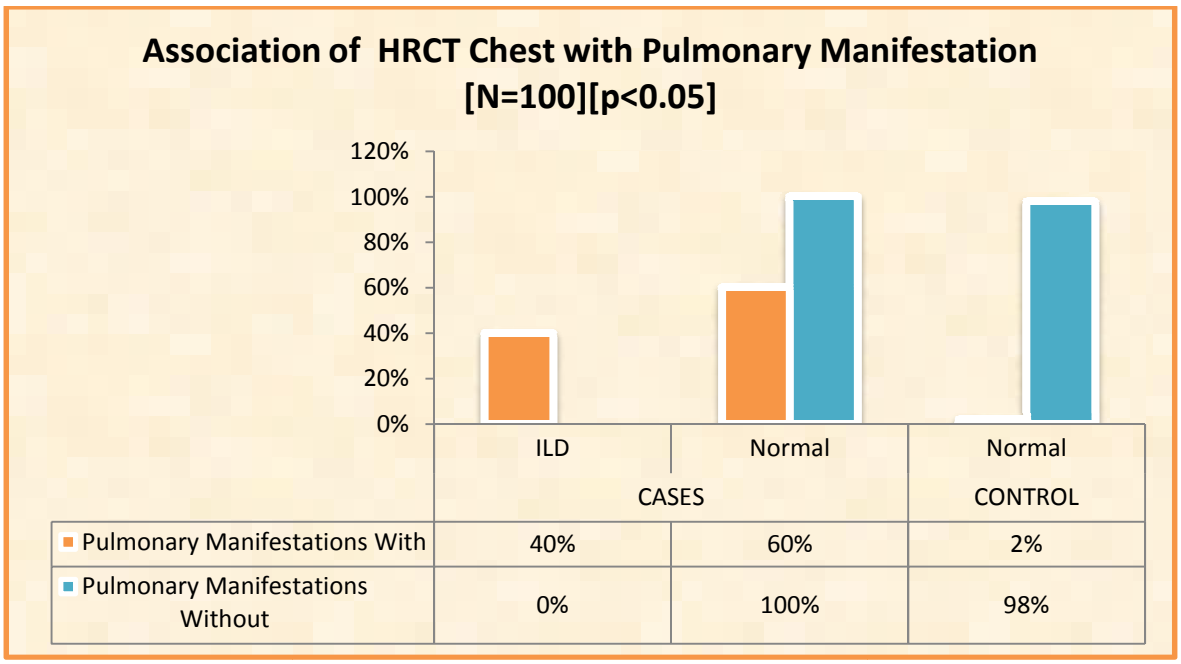
Association of HRCT with Pulmonary Manifestations in study Groups

STUDYGROUP	HRCT Chest	Pulmonary Manifestations		Total	(%)	Sig
		With	Without			
CASES	ILD	4	0	4	8%	<0.01
	Normal	6	40	46	92%	
	Total	**10**	**40**	**50**	**100%**	
CONTROL	Normal	1	49	50	100%	>0.05
	Total	**1**	**49**	**50**	**100%**	

Out of 10 patients with pulmonary manifestation,4 patients were showed lesions in HRCT chest.

Extremely Significant association of HRCT with pulmonary manifestation was observed in patients with ankylosing spondylitis with p value of < 0.01.

FIGURE: 25ASSOCIATION OF HRCT WITH PULMONARY MANIFESTATIONS IN STUDY GROUPS



Out of 10 patients with pulmonary manifestation, 40% were associated with ILD and 60% showed normal findings in HRCT chest.

TABLE:18MEAN CLINICAL VARIABLES IN EXPERIMENTAL CASES

Mean Clinical Variables in experimental cases

	Pulmonary Manifestation	Mean	SD	95% CI for Mean		Minimum	Maximum	Sig
				Lower	Upper			
Age	WITH	40.82	2.676	39.02	42.62	35	44	
	WITHOUT	37.98	3.357	37.27	38.68	32	46	<0.01
	Total	38.29	3.397	37.62	38.96	32	46	
Duration	WITH	10.7	1.16	9.87	11.53	9	13	
	WITHOUT	4.55	1.947	3.93	5.17	1	9	<0.001
	Total	5.78	3.073	4.91	6.65	1	13	
CRP	WITH	13	5.727	9.15	16.85	9	28	
	WITHOUT	11.54	6.752	10.12	12.96	3	30	>0.05
	Total	11.7	6.637	10.38	13.02	3	30	

In the study population, age distribution and duration of the disease has extremely significant association with the pulmonary manifestation with the P value of < 0.01.C- reactive protein having P value of >0.05 in the study .

Figure : 26 Mean age with pulmonary manifestation.

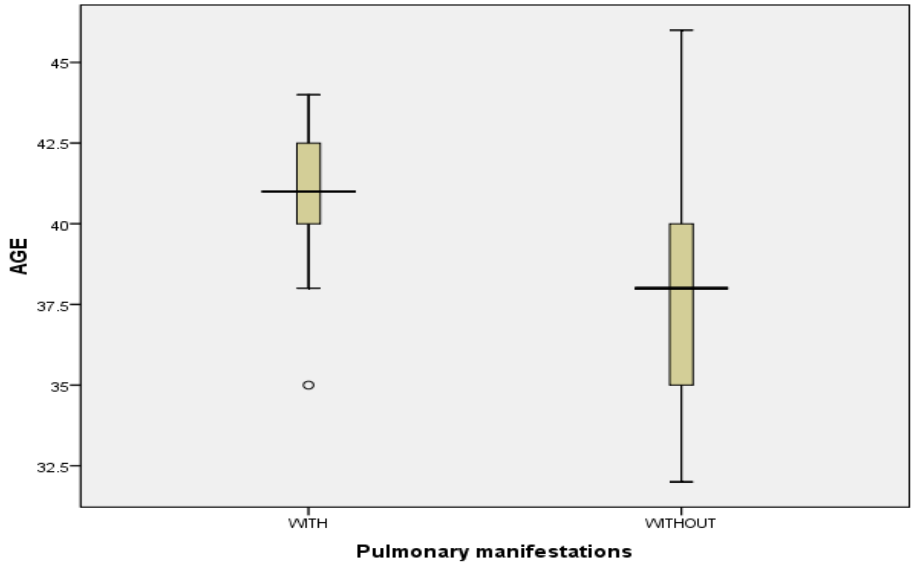


Figure : 27 Mean CRP with pulmonary manifestations.

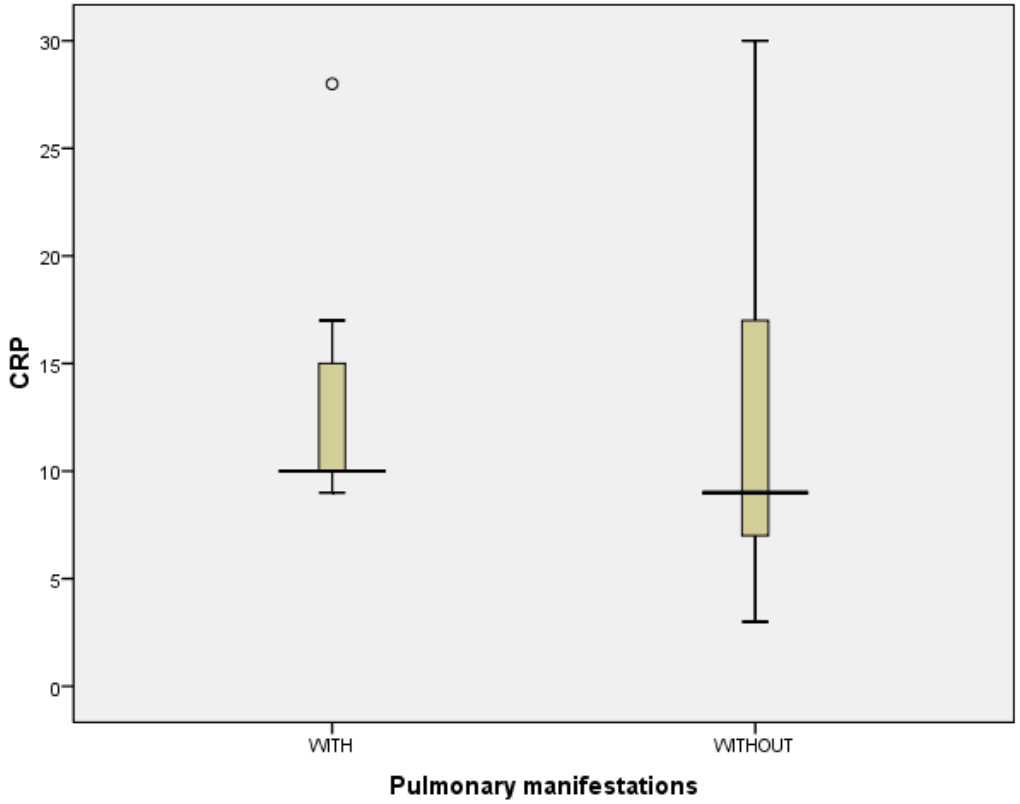
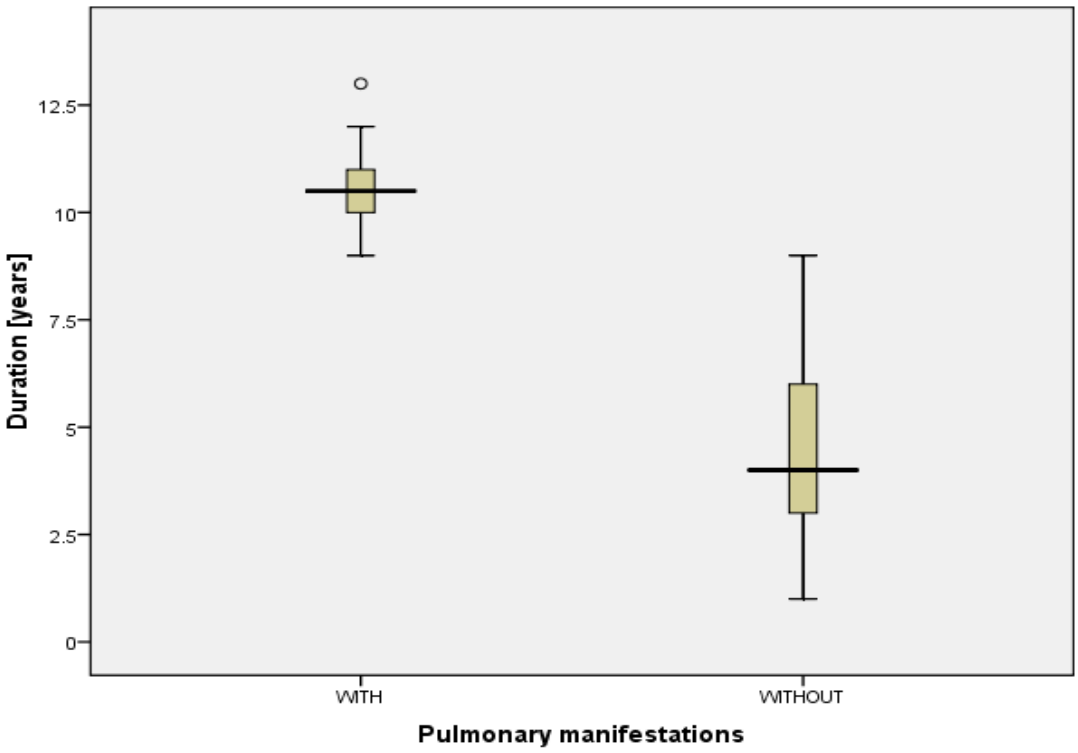


Figure:28 Mean duration with pulmonary manifestation.



DISCUSSION

Pulmonary involvement is one of the extra articular manifestation of ankylosing spondylitis .These manifestation have been documented in various studies using chest x- ray, pulmonary function test, and high resolution computed tomography of chest.

The study was conducted with 50 ankylosing spondylitis patients attending the rheumatology OPD in Coimbatore medical college hospital. Among the 50 patients, 76% were males and 24% were females .The male to female ratio in our study group was 3 : 1,which is similar to the findings in many studies . MahnazMomeni et al in which male are predominately affected than the female.

In our study , the age of the study population is 18- 60 years and the mean age of the study population is 38.29 years which is similar to the study done by vjollcakoko et al.

Prevalence of pulmonary manifestation among the ankylosing spondylitis in our study is 10 patients comparable to the study done by Abdellah E1 Maghraoui et al 2011 on extra articular manifestation of ankylosing spondylitis, in which they 55 patients studied had restrictive lung function in 16 persons and 29 patients had lesions in HRCT chest.

The study includes 50 ankylosing spondylitis patients and the pulmonary manifestation is studied using pulmonary function test and HRCT chest. Pulmonary function test of 10 patients showed abnormality. Out of this10 patients, 6 had mild restriction and 4 had moderate restrictive functions. Similar findings shown by studies done by Maghraoui et al.L R fisher et al 1990 studied 32 patients of ankylosing spondylitis and found that there is restrictive lung function and limitation of working capacity.

In our study, it showed interstitial lung disease in four patients out of 10 patients who had pulmonary manifestation of ankylosing spondylitis. I P Casserly, H M Fenlon, et al studied 26 AS patients and found 16 had abnormalities in HRCT chest like ILD and bronchiectasis.

In our study ,out of 50 patients of ankylosing spondylitis 10 patients had pulmonary manifestation . Out of 10 cases , 6 cases had pulmonary symptoms and 4 does not have any symptoms. These 4 cases are diagnosed by doing pulmonaryfunction test and HRCT chest . Therefore,pulmonary manifestation in subclinical cases is identified by doing these investigations in subclinical cases.

In our study there is no significant relationship between CRP and AS and the pulmonary manifestation.

In our study there has been association between the onset of disease and the pulmonary manifestation. There is a gender predilection in the pulmonary manifestation in ankylosing spondylitis patients. There was no correlation between CRP levels and the developmentof pulmonary manifestation.

There was significant association between the duration of the disease and the pulmonary manifestation in AS.

In our study 12% patients were with pulmonary symptoms and 88% were asymptomatic cases of ankylosing spondylitis. Hence, there is a significant association with the P value of <0.05.

SUMMARY

The study was conducted in ankylosing spondylitis attending rheumatology outpatient in Coimbatore medical college hospital in association with pulmonology department .The study analyses the pulmonary manifestation in ankylosing spondylitis. The study was conducted for the period of one year from July 2014 to July 2015.

The study population is between 18- 60 years and the mean age group of the population was 38.25 years.

In the study population, males are 74% and females 26% ,and it is in the ratio of 3: 1 ratio and has significant association .

Pulmonary manifestation is present as the late complication. 5 cases occurring within a duration 5-10years andanother 5 case occurring in less than 5 years. The duration of the disease as a significant association with the pulmonary manifestation.

In our study of 50 cases,only 6 cases had pulmonary symptoms accounting to 12% whereas 44 cases found to be asymptomatic. Pulmonary manifestation is found in 10 cases,therefore many 4 subclinical cases are present with pulmonary manifestation. Significant

association was observed with the duration of disease and the pulmonary manifestation.

The prevalence of pulmonary manifestation is about 10 cases(20%) out of 50 cases of ankylosing spondylitis. The pulmonary function test showed restrictive pattern in 10 cases. Mild restrictive pattern is seen in 6 cases and moderate restrictive pattern in 4 cases.

Interstitial lung disease were found in 4 cases using high resolution computerized tomography of chest out of 50 cases of ankylosing spondylitis. Significant association was observed in the occurrence of pulmonary manifestation in using HRCT chest.

CONCLUSION

Pulmonary manifestation is one of the extra articular manifestation in patients with longstanding ankylosing spondylitis .

As there is no clear guidelines regarding step-wise approach to screen patients with pulmonary manifestation. While with improved techniques like pulmonary function test and HRCT chest allows early detection of pulmonary manifestation of the disease.

Hence, early detection of pulmonary disease can change the prognosis and also provide concrete data which allows to recommend early pulmonary testing in ankylosing spondylitis.

BIBILIOGRAPHY

1. 1.Harrison's Principles of Medicine, 18 th edition, Chapter 325.
2. EI Marghraoui ,A.Ankylosing spondylitis .Presse med. 2004;33:1459-1464.
3. Youssef W,Russell AS.Cardiac,ocular,and renal manifestations of seronegative Spondyloarthropathies.Curr Opin Rheumatol 1990;2:582
4. Calin A, Fries JF. Striking prevalence of ankylosing spondylitis in "healthy''w27positive males and females A controlled study. New England Journal of medicine 1975;835-839
5. N.kanathhhur and .Lee-chiong , " Pulmonary Manifestations of Ankylosing Spondylitis,"clinics in Chest bMedicine, vol.31,no.3pp.-554,2010.
6. W.m.Rumanick, H. Firooznia, M. S. Davis Jr.et.al., "Fibrobullous disease vof the upper lobe ; an extraskeletal manifestation of ankylosing spondylitis,''Journal of Computed Tomography,vol.8no,3pp.225-229,1984.
7. D.Davies', "Lung fibrosis in ankylosing spondylitis," Thorax,vol.27,no.2p.262,1972.
8. D.Thai,R.s.Ratani,S.Salama,andr.M.Steiner, "Upper lobe fibrocavity disease in a patient with back pain and stiffness,"Chest,vol.118,no.6pp.1814-1816,2000.
9. Journal of Rheumatology,vol.36,no.2,no.

10. 10.H.H.Ho,M.c.Lin,K.h.Yu,C.MwANG,y.j.jWu, and j.L.Y Chen,tuberculosis anddisease –related pulmonaryapical fibrosis in ankylosing spondylitis," Journal of Rheumatology,vol.36,no.2, pp.355-360,2009.

11. L.T. Tanoue, pulmonary Involvement in collagen disease vascular:a review of the pulmonary maniestationof theMarfan syndrome,ankylosing spondylitis Sjogrenm syndrome,a nd relapsing polychondritis,journal of Thoracic Imaging,vol.7, no.2.pp62-77,1992.

12. A.A.Cohen,E.aNatelson,R.E.Frechner et al."Fibrosing interstitial pneumonitis in ankylosing spondylitis ,''Chest,vol.59, no.2pp.369-371,1971.

13. A.EI Maghraoui, S. Chaouir, A .Abid et al ., Lung findings on thoracic high –resolution computed tomography in patients with ankylosing spondylitis.Correlations with disease ,duration,clinical findings and pulmonary function testing,''Clinical Rheumatology , vol.23 , no.2 pp 123 -128 , 2004.

14. American Thoracic Society (ATS) Statement on standardization of Spirometry – 1994 update. Am j Crit care MED 1995 , 152;1107-1136.

15. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment ? Chest. 1999;115:869-873.doi: 10.1378/chest.115.3.869.

16. Gunnhild Berdat, Silje Halvorsen, Desiree van der Herijde, Morten Mowe, and Hanne Dagfinrud. Restrictive pulmonary function is more prevalent in patients with ankylosing spondylitis than in

matched population controls and is associated with impaired spinal mobility : a comparative study. doi 10.1186/ar3699.

17. Mahnaz Momeni, Nora Talyor , and Mahsa Tehrani. Cardiopulmonary Manifestations of Ankylosing Spondylitis. International Journal of Rheumatology. doi.10.1155/2011/728471

18. R.M.Stewart, J.B.Ridyard, and J.D.Pearson. Regional lung function in ankylosing spondylitis. Thorax (1976) , 31, 433-437.

19. S.Garrett, T.Jenkinson, L. G. Kennedy, H.Whitelock, P. Gaisford, and A. Calin, " A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index", Journal of Rheumatology, vol.21, no. 12,pp.2286-2291,1994.

20. C.K. Tan, C. C. Lai, C. H. Chou, and P. O. R. Hsueh, " Mycobacterium celatum pulmonary infection mimicking pulmonary tuberculosis in a patients with ankylosing spondylitis", International Journal of Infectious Disease, vol. 13, no. 6, pp e459-e462, 2009.

21. Oostveen J PrevoR al. Early detection of sacroillitis on magnetic resonance imaging subsequent development of sacroilitis on plain radio graphy . A prospective ,longitudinal study J Rheumatol 1999:26 ;1953 -8.

22. Braun J Bollow M,et al. Use of dynamic magnetic resonance imaging in the detection of early and advanced sacroilitis in spondylarthropathy patients . Arthritis Rheum 1994 :37 ;1039-45.

23. Dougdas, M ,Beheir JM Jolchnie I ,Calin A van der Heijde D , Olivieri I et al . Efficacy of celecoxib, a cyclooxygenase 2- specific inhibitor , in the treatment of ankylosing spondylitis ; a non-

steroidal anti-inflammatory drug . Arthritis Rheum 2001;44(1);180-5.

24. MelianA ,van der Heijde DM,James MK.Etoicoxib in the treatment of ankylosing spondylitis (AS).Arthritis Rheum 2002;46;s432

25. A.K. Sil, " Lung fibrosis in ankylosing spondylitis", Chest , vol. 61, no.4, pp.406-407, 1972.

26. U. Dincer, E. Cakar, M. Z. Kiralp, E. Bozkanat, H. Kilac, and H. Dursum, "pulmonary involvement in rheumatic disease: pulmonary effects of ankylosing spondylitis and its impact on functionality and quality of life", Tohoku Journal of Experimental Medicine, vol.212, no.4, pp.423-430, 2007.

27. Rudwaleit M, Listing J, Brandt J, et al: Prediction of a major response (BASDAI 50) to tumour necrosis factor alpha blockade in ankylosing spondylitis. Ann Rheum Dis 2004;63:665-670.

28. Anderson J, Baron G, van der Heijde D, et al: Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876-1886.

29. Wanders A, van der Heijde D, Landewe R, et al: Nonsteroidal anti-inflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis. Arthritis Rheum 2005;52:1756-1765.

30. Zochling J: Current evidence for the management of ankylosing spondylitis: A systemic literature review for the ASAA/EULAR management recommendations in AS. Ann Rhem Dis 2006;65:423-432.

31. Doran M, Brophy S, Mackay K, et al: Predictors of longterm outcome in ankylosing spondylitis. J Rheumatol 2003;30:316-320.

32. Rudwaleit M, Khan M, Sieper J: The challenge of diagnosis and classification in early ankylosing spondylitis: Do we need new criteria? Arthritis Rheu.

33. Zeboulon N, Dougados M, Gossec L: Prevalence and characteristics of uveitis in spondyloarthropathies: A systemic literature review. Ann Rheum Dis 2008;67:955-959.

34. Boushea D, Sundstrom W: The pleuropulmonary manifestations of ankylosing spondylitis. Semin Arthritis Rheum 1989;18:277-281.m 2005;52:1000-1008.

35. AUSTRALO-ANGLO-AMERICAN SPONDYLOARTHRITIS CONSORTIUM(TASC) et al: Geneome –wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet 42:123, 2010.

36. BROWN MA: Genetics and pathogenesis of ankylosing spondylitis. Curr Opin Rheumatol 21:318,2009.

37. Dougados M et al: The European Spondyloarthropathy Study Group preliminary for the classification of spondylorathropathy. Arthritis Rheum 34:1218,1991.

38. Braun J, Bollow M, Remlinger G, et al: Prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 1998;41:58-67.38.

39. Benjamin M : Microdamage and altered vascularity at the enthesis-bone iinterface provides an anatomic explanation for bone

involvement in the HLA-B27 associated spondylarthritides and allied disorders. Arthritis Rheum 56:224,2004.

40. Zeboulon N, Dougados M, Gossec L: Prevalence and characteristics of uveitis in spondyloarthropathies: A systemic literature review. Ann Rheum Dis 2008;67:955-959.

41. Kanathur N, Lee – Chiong T, “Pulmonary manifestation of ankylosing spondylitis”, clin chest Med.2010 sep;31(3):547-54.

42. Rudwaleit M: How to diagnose axial spondyloarthritis early. AnnRheu Dis 2004;63:535-543.

PROFORMA

Name :

Age :

Sex :

Address:

IP / OP No :

Hospital :

HISTORY:

ANKYLOSING SPONDYLITIS

Low back ache

Bony tenderness

Joint involvement

Duration of disease

EXTRA ARTICULAR MANIFESTATIONS:

Malaise,fatigue,low grade fever

Hemoptysis,Cough,dyspnoea,chest pain,wheeze.

Ocular symptoms

Skin lesions

Muscle weakness, nerve involvement.

Diarrohea,and other GIT symptoms

TREATMENT HISTORY:

PHYSICAL EXAMINATION;

GENERAL EXAMINATION:

Pulse - BP- RR- .

Pallor/ pedal oedema /lymphadenopathy/icterus.

SYSTEMIC EXAMINATION:

RESPIRATORY SYSTEM

Inspection

Palpation

Percussion

Auscultation

CARDIOVASCULAR

ABDOMINAL

NEUROLOGICAL

RHEUMATOLOGICAL

JOINTS INVOLVED.

INVESTIGATIONS:

Haemoglobin; WBC Platelet Count

ESR CRP

RFT LFT

CHEST X-RAY

PULMONARY FUNCTION TEST

HRCT - CHEST

CONSENT FORM

You, Shri./ Smt./ Kum. _____, aged ____ years, S/o / D/o / W/o _____, residing at _____ _____ are requested to be a participant in the research study titled '***Study on Pulmonary Manifestations in Ankylosing spondylitis***' in Government Medical College Hospital, Coimbatore, conducted by Dr. R.Nithyakalyani, Post Graduate Student in the Department of General Medicine, Coimbatore Medical College. You satisfy eligibility criteria as per the inclusion criteria. You can ask any question or seek any clarifications on the study that you may have before agreeing to participate.

RESEARCH BEING DONE

'**STUDY ON PULMONARY MANIFESTATIONS IN ANKYLOSING SPONDYLITIS**'

PURPOSE OF RESEARCH

- To observe the pulmonary manifestations of various Ankylosing spondylitis patients by pulmonary function test and chest X- ray, collect the data, and to analyse the same
- To investigate the correlation between ankylosing spondylitis and cardiac diseases

- To find out the relation, if any, between pulmonary lesions with the degree, severity and duration of RA

PROCEDURES INVOLVED

The research includes detailed clinical examination including medical history, physical examination.

DECLINE FROM PARTICIPATION

You are hereby made aware that participation in this study is purely voluntary and honorary and that you have the option and the right to decline from participation in the study.

PRIVACY AND CONFIDENTIALITY

You are hereby assured about your privacy. Privacy of subject will be respected and any information about you or provided by you during the study will be kept strictly confidential.

AUTHORIZATION TO PUBLISH RESULTS

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified; neither will your privacy be breached.

STATEMENT OF CONSENT

I, _____, do hereby volunteer and consent to participate in this study being conducted by Dr. R.Nithyakalyani. I have read and understood the consent form / or it has been read and explained to me. The study has been fully explained to me, and I may ask questions at any time.

Signature / Left Thumb Impression of the Volunteer Date:

Signature and Name of witness Date: